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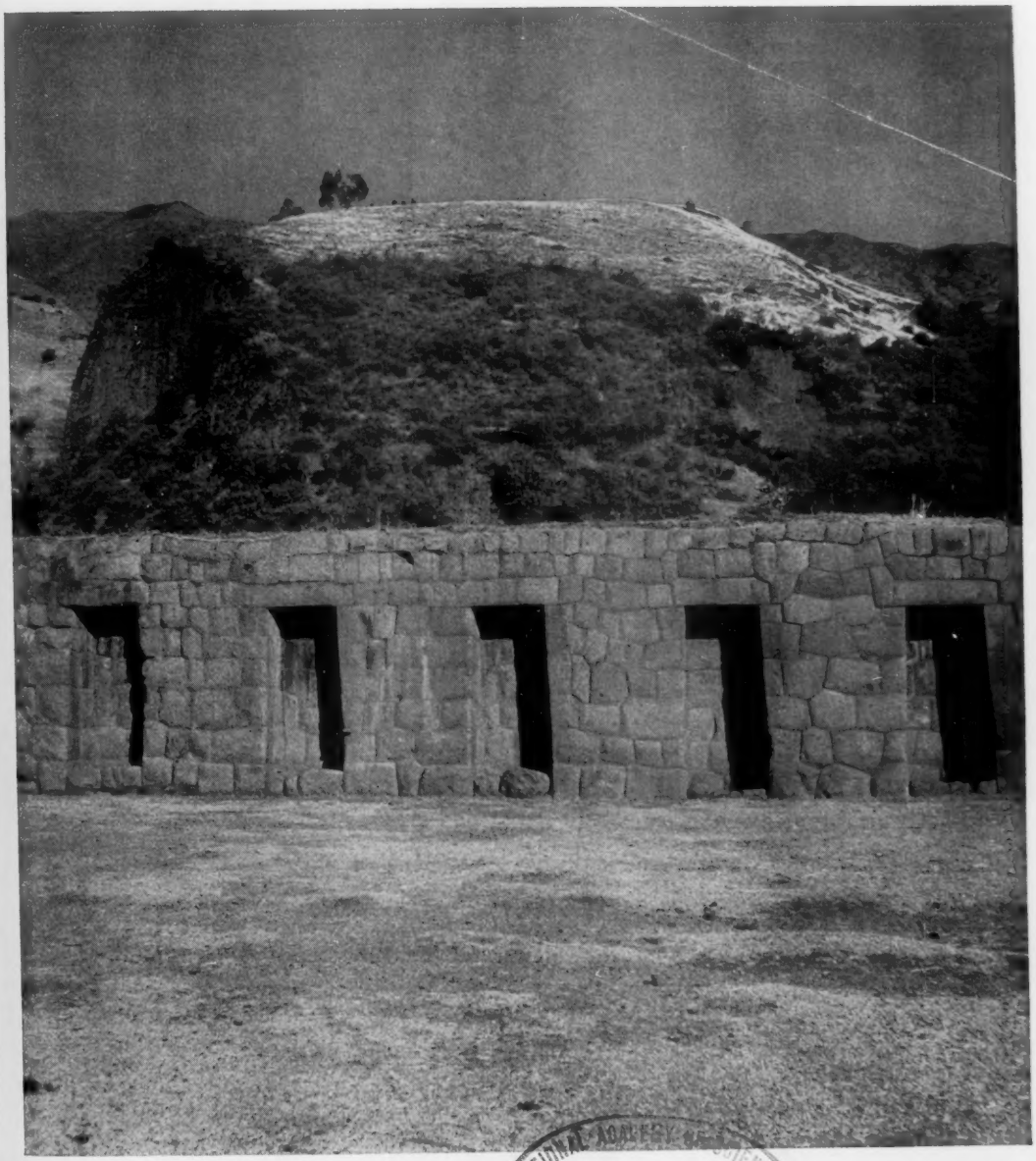

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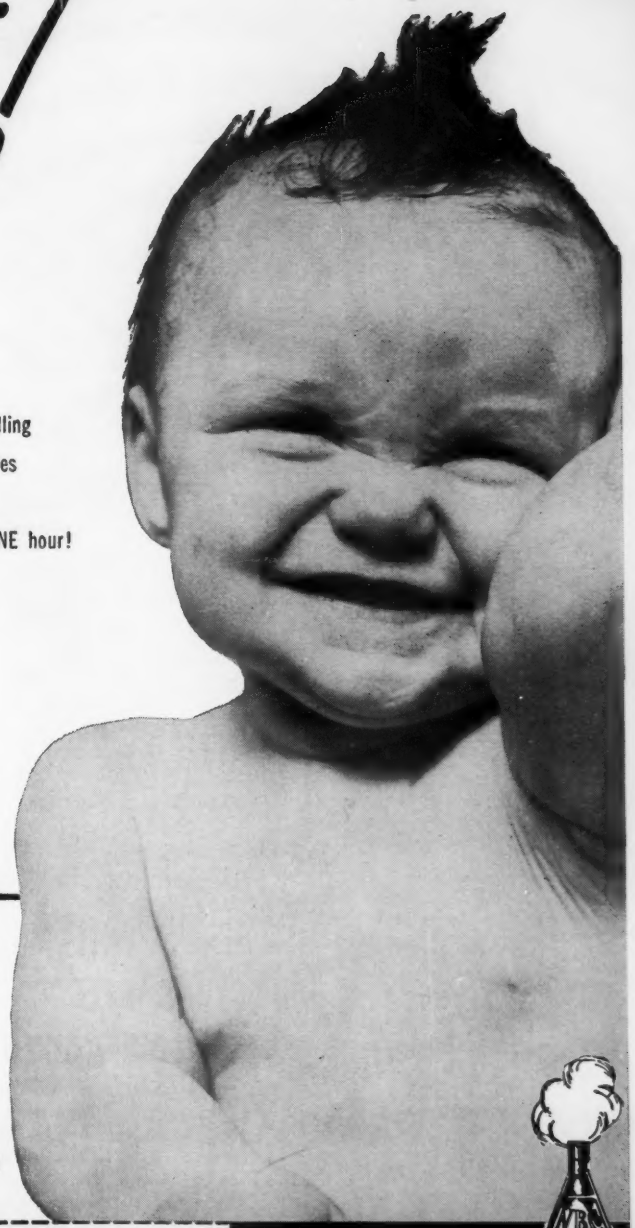

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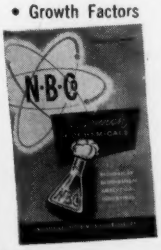

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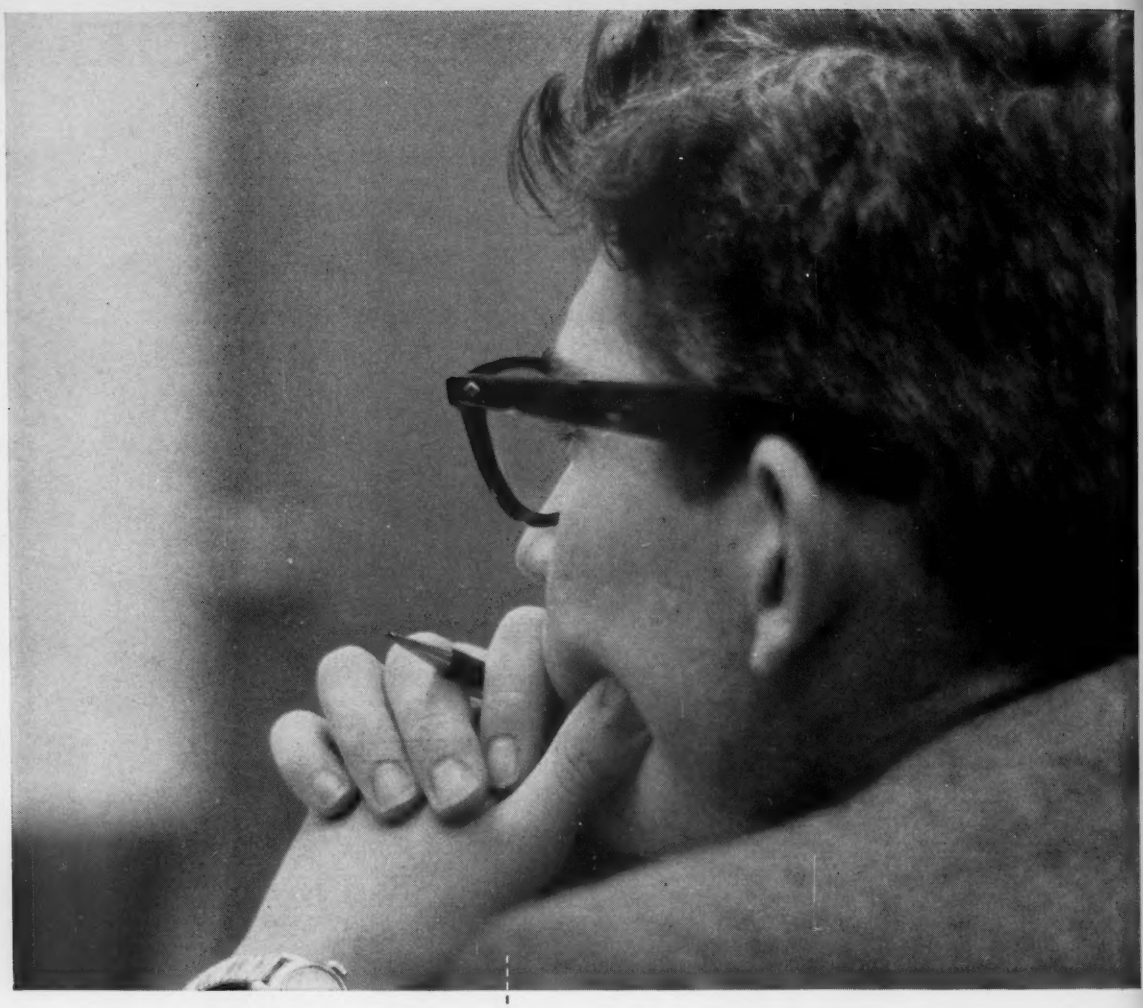
The remains of the "speaking river" tambo, one of the royal stations on the Royal Road of the Incas between Cuzco and Quito. Called "Rimac-tampu" in Incan times, this was the way-stop before the "Speaking Apurimac River." From *The Incas of Pedro Cieza de León*, reviewed by Gordon R. Willey on page 973. [Courtesy University of Oklahoma Press]



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Editorial and personnel-placement correspondence should be addressed to SCIENCE, 1515 Massachusetts Ave., NW, Washington 5, D.C. Manuscripts should be typed with double spacing and submitted in duplicate. The AAAS assumes no responsibility for the safety of manuscripts or for the opinions expressed by contributors. For detailed suggestions on the preparation of manuscripts and illustrations, see *Science* **125**, 16 (4 Jan. 1957).

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After 20 Years—Technicians or Scholars?

As teacher education programs are strengthened and teacher certification requirements are made more demanding of aptitude, scholarship, and subject-matter competence, we will produce an increasing and permanent supply of highly competent teachers. Or will we? When does teacher education stop? With a bachelor's degree? A master's degree? More simply, when should a science teacher stop learning about science? When can a teacher stop being also a student?

The answer, of course, is never! Formal academic degree programs should be considered as basic preparation for the teaching profession and the beginning of a self-determined, self-disciplined program of continuing improvement in both subject-matter competence and teaching skills. Career-long dedication to self-improvement is one of the outstanding characteristics of a "professional," be he science teacher or research scientist.

Too often young science teachers with up-to-date subject-matter training but no teaching experience develop into mature science teachers with extensive teaching experience but no up-to-date information. This constitutes a waste of talent equal to and perhaps even greater than that resulting from inadequate formal preparation. Far too many teachers "retire" long before they stop teaching. Other things being equal, the mature teacher should be the most competent teacher, the "master teacher," not simply an efficient and skillful "educational technician" but a scholar, a serious student of his own subject.

Unfortunately, there is almost no community interest in or genuine recognition of continuing teacher self-improvement beyond formal degree programs. We have allowed teachers to become so burdened with nonprofessional, nonacademic, and nonscholarly duties that they have neither the time nor the enthusiasm for rigorous intellectual rejuvenation. We are now well beyond affording the luxury of wasted professional talent—well beyond the efficacy of "pumping the well dry."

Recent programs are making great strides in providing opportunities for teachers to again become students of their subject-matter areas through summer institutes, refresher courses, research participation programs, in-service training courses, and television courses such as Continental Classroom's "Modern Chemistry" and "Atomic Age Physics." Not long ago only single teachers could afford several nonremunerative summers on a college or university campus. Now the opportunity for refresher and advanced training is becoming increasingly available to all teachers. Whether they take advantage of these opportunities, however, depends on the incentives, inspiration, interest, encouragement, and recognition that can be transmitted to teachers by their colleagues and members of the school community.

We need to develop an intellectual atmosphere at the community level that encourages and recognizes scholarship on the part of both teachers and students; an atmosphere that encourages science-teacher participation in the activities of professional educational organizations as well as professional scientific organizations; an atmosphere that allows more time for study, laboratory preparation, guidance of science projects, participation in research, development of equipment and visual aids, course revision, and similar scholarly activities; an atmosphere that returns to the teacher the role of scholar rather than technician.

Teacher education is a complex subject involving many factors, including money and time; it must not be shortened by falsely assuming that it ends with formal college training or that local school administrators and citizens have no responsibility for an important part of it.—R. E. HENZE, *American Chemical Society*.

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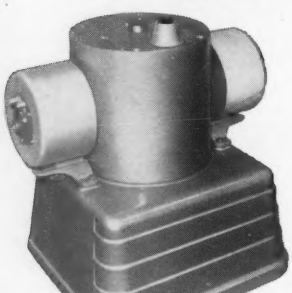

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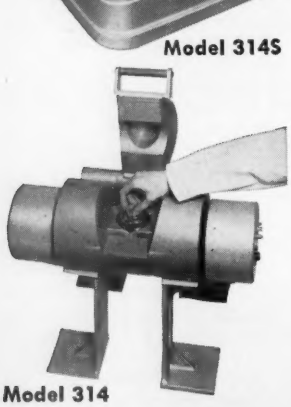

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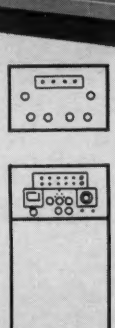

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CURRENT PROBLEMS IN RESEARCH

Reactions of Grafts against Their Hosts

Transplantation immunity works both ways—hosts destroy grafts and grafts may harm hosts.

R. E. Billingham

Even the layman is now aware that, with the exception of one or two tissues such as cornea and cartilage to which special dispensations apply, organ or tissue grafts transplanted from the body of one person to that of another do not normally survive in their new host for longer than a week or two. In man, only identical twins are excepted from this generalization. There are now several cases on record where one twin has successfully given a sound kidney to replace the diseased and nonfunctioning kidneys of the other.

This state of affairs is certainly not peculiar to man, for it obtains in all vertebrates so far investigated: frogs, goldfish, chickens, rats, mice, rabbits, squirrels, dogs, and monkeys, to mention only a few animals in the now formidable list. The demise of *homografts*, as grafts of tissues or organs transplanted between genetically unrelated individuals of the same species are known, is certainly not attributable to inadequacies of grafting procedures, such as temporary interruption of blood supply. This has been repeatedly demonstrated by comparing the short duration of homografts with the successful survival of *autografts* of the same tissue —that is, grafts donated by an animal to itself.

In grafting complex and relatively large organs, such as kidneys, it is of course obligatory to couple up the main blood vessels with those of the host at the operation if the grafts are to stand any chance of survival. With small grafts, on the other hand, such as thin sheets or pieces of skin or fragments of ovarian tissue, close approximation with living, freshly exposed and vascularized mesenchymal tissues of the host is all that is necessary. The juxtaposed graft and host tissues soon become knit together through the activity of fibroblasts, and revascularization—another facet of the healing process—is accomplished within a day or two as the consequence of a sort of end-to-end union between some of the small severed vessels of the graft and those of the host tissue.

Because of the ease with which they may be transplanted and their subsequent accessibility for observation and removal for histological study, skin homografts have been studied most extensively. With very few qualifications the conclusions reached from these studies appear to hold good for homografts of other normal tissues and of solid, malignant tissues transplanted to many different sites in the body.

Immunological Nature of Homograft Rejection

One of the most fundamental advances in homograft research was Medawar's unequivocal demonstration in 1944 that skin homograft incompatibility is not innate but is an immunological phenomenon. All homografts enjoy at least a short period of well-being during which they are almost impossible to differentiate from autografts. The duration of this period depends upon the amount of foreign tissue grafted: small homografts usually live longer than large ones, though this dosage effect is weak. The onset of inflammation and swelling in a skin homograft, accompanied at the microscopic level by an infiltration of its dermis by leucocytes (mainly lymphocyte-like cells) from the host, the eventual cessation of its blood supply and its rapid deterioration to a necrotic scab, are all direct or indirect consequences of the host's immunological reaction (the so-called homograft reaction) against the foreign cellular antigens present in the graft. One of the best expressions of the intensity or severity of the host's response is the survival time of the graft.

Individuals that have reacted against solid tissue homografts, or against cellular homografts such as leucocyte or spleen cell suspensions injected intravenously or by other routes, are sensitized so that subsequent homografts from the original donor, or from another of similar antigenic constitution, undergo an accelerated destruction. With skin homografts this summary rejection frequently goes hand in hand with failure to heal in properly. This "second-set" phenomenon at present constitutes the only test applicable to *all* species for determining whether a given type of tissue homograft, cell suspension, or extract prepared therefrom has sensitized a recipient. That there is no cellular or tissue specificity involved in tissue transplantation immunity was suggested by a body of evidence showing that the sensitization evoked in a recipient by one type of tissue or cellular homograft is fully effective against subsequent homografts of other types of tissue from the same donor. More recently, analyses making use of the principle of immunological tolerance (see below) have shown that *all* living tissue cells of the body of a given individual must have identical

The author is a member of the Wistar Institute of Anatomy and Biology, Philadelphia, Pa.

complements of the cellular antigens responsible for transplantation immunity.

Genetic Determination of Transplantation Antigens

The most valuable tools for the analysis of homograft incompatibility, and those which revealed at an early date that it was genetically determined, are the many different inbred or *isogenic* (genetically uniform) strains of mice. These have been produced by many consecutive generations of brother-sister matings. With one important qualification mentioned below, *isografts* (grafts exchanged between members of the *same* inbred strain) are permanently successful, like grafts exchanged between a pair of identical twins, since they all have exactly the same genes and consequently the same gene-determined cellular transplantation antigens. In recent years, following the pioneer work of C. C. Little, combined genetic and transplantation studies have shown that the antigenic substances responsible for eliciting homograft reactions between *different* isogenic mouse strains are determined by multiple dominant Mendelian genes—known as *histocompatibility* genes—and that there are at least 15 different genetic loci involved, though only three of these have been subjected to analysis. The most important of this trinity is the so-called H-2 locus, which may be tenanted by not less than 10 alleles or alternative genes. Some of the alleles determine the formation of transplantation antigens so powerful that hosts which differ from their donors simply at this one locus—that is, with respect to a single antigen—may destroy a homograft within less than two weeks.

Provided that the entire complement of genetically determined transplantation antigens possessed by a homograft is also fully represented in the host's own complement, that graft will survive indefinitely like an autograft or an isograft since it fails to confront the host with anything that is "foreign" to it. The F_1 hybrid animals produced by mating parents from two *different* inbred homozygous strains are highly important, as we shall see later. Since each hybrid receives a set of chromosomes from both of its parents, it has all the histocompatibility genes, and therefore the transplantation antigens, present in each parental strain. Consequently, hybrid animals are incapable of reacting against homografts from either of the parents. It will be noted, however, that a parental strain graft on an F_1 hybrid host itself lacks those antigens of the host which the latter derived from the other parent. For this reason, F_1 hybrid grafts are acceptable to neither parental strain (see Fig. 1).

In addition to the three histocompatibility loci referred to above, there is one other, known to be present in both mice and rats, which seems to provide a transplantation immunity system of exquisite simplicity. Males differ genetically from females in that they possess a Y chromosome which the females lack, and the data at present available strongly suggest that a weak transplantation antigen is determined by a locus present on that chromosome. Males will accept isografts from male or female donors, but females normally reject isografts from male donors. In the C57BL mouse strain the median expectation of survival of male skin isografts on females is about 27 days. It has been shown that this factor is present in and determines exactly the same antigen in all male mice so far tested, irrespective of their strain, though for some reason not all females are capable of responding to it.

Merely to say that homograft incompatibility is a genetically determined immunological phenomenon is not enough. To conclude this very brief introductory account of the immunology of homograft rejection it is necessary to say a little about the type of immunological response involved and the nature of the postulated cellular transplantation antigens which provoke it.

Cellular Nature of Transplantation Immunity

The body's immunological defense mechanism usually responds to invasion by foreign microorganisms or to inoculation with foreign antigens such as bovine serum albumen or sheep red blood cells (which immunologists frequently employ) by the production of specific antibodies—protein molecules which are elaborated in the lymphoid tissues and are present in the globulin fraction of the serum. Directly or indirectly these products of the immunological reflex lead to the inactivation and elimination of the particular agent which evoked their formation. However, despite the fact that serum antibodies are formed in response to tissue

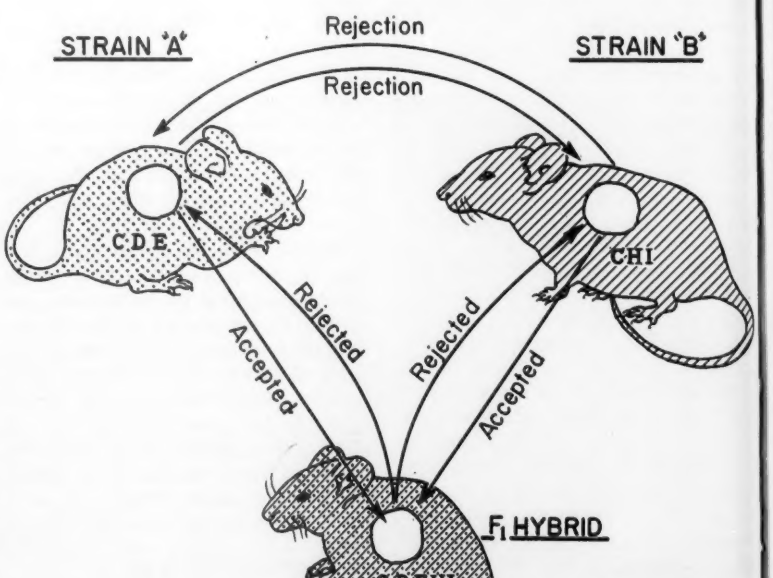

Fig. 1. Fates of skin homografts exchanged between mice of two different inbred strains and their F_1 hybrid. The hypothetical transplantation antigens of these parental strain mice are indicated by the letters *CDE* and *CHI*. Since it receives all the genes present in both parents, the antigenic constitution of the hybrid animal will be *CDEHI*. Only those homografts are accepted which have no antigens that are not also represented in the host.

Fig. 2. Mouse bearing a skin homograft, *G*, from which antigenic material escapes and reaches the draining or regional lymph node (R.L.N.) via the afferent lymphatic vessels (A.L.V.). The antigens stimulate the production of immunologically activated cells which leave the node via the efferent vessels (E.L.V.) and so reach the blood stream. They are carried to the homograft, infiltrate its substance, and bring about its destruction.

homografts—they can be revealed by their ability to agglutinate the donor's red blood cells—there is no convincing evidence that these antibodies are in any way responsible for the destruction of homografts of skin or other solid tissues. (They may, however, be the agents of destruction of cellular homografts of lymphocytic cells and of certain types of leucotic and ascites tumors.) For example, serum prepared from the blood of animals which have rejected homografts will not bring about the accelerated rejection of appropriate test tumor or skin homografts if it is transferred to other "virgin" mice of the serum donor's own strain.

As N. A. Mitchison was first to demonstrate, transplantation immunity can be transferred from one animal to another only by means of lymphoid cells prepared from the lymph nodes or the spleen of a sensitized animal. As studies with more familiar types of antigens have established, these organs and the scattered and less clearly defined foci of lymphoid tissue which are present in most other organs and tissues of the body contain those cells which can manufacture antibodies—that is, *immunologically competent* cells, which I shall refer to hereafter noncommittally as lymphoid cells. All the evidence at present available is consistent with the view that the homograft reaction is called into being by the passage of antigens from the graft via the draining lymphatic vessels to the regional lymph nodes where they stimulate the production of immunologically activated cells which resemble the lymphocytes of the blood. These activated cells then leave their site of origin, and after passage through the blood stream infiltrate the homografts for whose destruction they are ultimately responsible (Fig. 2). Some authorities believe that these cells are the vehicles for fixed antibodies which are bound to their surfaces and that these are the antibodies responsible for destroying the homografts. However, it must be emphasized that the actual mechanism whereby these "sensitized" cells bring about graft destruction still awaits experimental elucidation. Other types of *cell-mediated*, as opposed to circulating-antibody-mediated, immunological responses are known: they include the tuberculin reaction and allergies to certain chemicals.

Chemical Nature of the Antigens

The nature of the antigenic substances responsible for transplantation immunity has long been a provocative question, especially since even the most conservative methods of killing cells or tissues completely destroy their ability to sensitize if they are grafted or injected. Recently it has been shown that despite their lability, antigenically active substances can be extracted in aqueous solution from living tissue cells of mice and guinea pigs. Preliminary analysis indicates that their determinant groups are amino acid polysaccharide complexes.

Reaction of Grafts against Homologous Animals

So far we have been exclusively concerned with a survey of what is known about the destructive forces which are brought into action when an animal is confronted with a graft of homologous tissue. The primary purpose of this article, however, is to give an account of a new aspect of transplantation immunology: the situation in which, at least in an immunological sense and as a consequence of various experimental artifices, the roles of host and graft are reversed.

In 1953 Dempster and Simonsen, studying the fate of kidney homografts in dogs, independently observed cytological changes in the reticuloendothelial cells (lymphoid-type cells) present in these organs which they postulated might be indicative of antibody formation against the antigens of the host. This hypothesis was perfectly plausible: being continuously perfused with the foreign (from their point of view) blood of the host, the grafted kidneys were certainly thoroughly exposed to an antigenic stimulus. Unfortunately these homografted organs were destroyed by the conventional homograft reaction long before more convincing evidence could be obtained of their possible counterattack against the hosts.

From what has already been said in the introduction, it follows that for a graft to be able to launch and sustain an immunological attack on its recipient there are at least three prerequisites: first, it must contain mature immunologically competent cells; second, the host must possess important transplantation antigens (histocompatibility genes) which are lacking in the graft, so that the host appears foreign to it; and third, the host must itself be incapable of reacting against the graft, at least for a long enough time for the latter to manifest its immunological capabilities—like some Sinbad forced to endure the insults of an Oid Man of the Sea whom he cannot dislodge from his shoulders.

During the last few years several different means have been forthcoming for making animals completely or at least temporarily incapable of rejecting tissue or cellular homografts so that they become graft or cellular chimeras, thus fulfilling one of the essential conditions for the revelation of graft-versus-host reactions.

"Runt Disease" in Immunologically Tolerant Animals

It was long believed that embryos or very young animals are incapable of immunological responses, largely on the basis of such empirical facts as the almost universal hospitality of avian embryos to foreign tissue grafts or

microorganisms and the inability of very young animals to form antibodies. Investigations in which living homologous cells were inoculated into embryonic or newborn mice, chickens, and animals of other species have shown that the hosts may in fact respond to these antigens—by becoming *tolerant* of them. To quote one example: if a newborn A strain mouse is injected intravenously or intraperitoneally with a suspension of spleen cells prepared from a CBA strain donor, then when the A strain mouse grows up it will be found to be incapable of reacting against a skin or other tissue homograft from the CBA donor strain. Furthermore, as immunological tests have shown, the splenic cells which called the tolerant state into being show a remarkable "homing" instinct, for they appear to settle out electively in, and so become foreign residents of, anatomically appropriate tissues of the new host—that is, its various lymph nodes, its thymus, spleen, bone marrow, and almost certainly all the small aggregates of lymphoid tissue which are present in most organs of the body. This state of acquired immunological tolerance is highly specific; it extends only to subsequent tissue homografts having the same antigenic constitution as the initial neonatal inoculum, and it depends upon the inability of the host's lymphoid tissues to become sensitized to the antigens to which they were exposed at an early state of their development.

The actual mechanism of immunological tolerance, like the mechanism of antibody formation, is still in the realm of speculation. The principle of tolerance certainly applies to antigens of many different kinds. Its present significance is that it affords one means of enforcing acceptance of homografts upon a host.

In our initial studies on the induction of tolerance in newborn mice with adult splenic cells, L. Brent and I were particularly lucky in our selection of strains CBA and A. The postoperative mortality of our hosts was low, and most of the tolerant animals remained outwardly normal. However, the lymphoid organs of nearly all these animals manifested at least some degree of hypoplasia, a fact which for a while we were at a loss to explain. With other strain combinations, however, and particularly with those which probably differed from their donors with respect to powerful transplantation antigens determined by the H-2 locus, it was observed that many of the mice stopped growing within a week or two of injection, became emaciated, and usually suffered from diarrhea (Fig. 3). Most of the mice thus affected died within a few days, but some lingered on for two or three months as chronically sick and grossly stunted individuals with abnormally sparse fur (Fig. 4). Apart from impairment of growth, the most striking and constant symptom of "runt" disease, as we christened it, was the widespread involution of lymph nodes and the lymphoid or Malpighian centers in the spleen, though frequently distinctive lesions in the liver were observed.

Fig. 3. Three 12-day old "A" strain mice. The two on the left were injected at birth with splenic cells from an adult C57 strain mouse and are now very sick and emaciated. Their uninjected littermate, on the right, is perfectly healthy.

Several different lines of evidence suggested that this disease was the outcome of a reaction on the part of immunologically competent cells, introduced in the neonatal inoculum, against the antigens of the host. Presumably the foreign antigens of the host, confronting these cells in the milieu in which they had settled out (the host's own lymphoid tissues), stimulated them to proliferate and so add weight to the immunological attack. It is almost inconceivable that a dosage of a million splenic cells—all that is necessary to cause fatal runt disease with some strain combinations—is in itself sufficient to do the damage. To cite only a little of the evidence that runt disease is the expression of a graft-versus-host reaction: The severity of the disease is greatest when the donor and host strains are most distantly related genetically, and no symptoms of runt disease are detectable if the donor and recipient strains are very closely related. The severity of the disease is heightened, as one would expect, if splenic cells, instead of being taken from a "virgin" adult donor, are taken from a donor which has previously been sensitized against the cellular antigens of the intended recipient. Finally, and most important, is the fact that runt disease does not appear if splenic cells from an F_1 hybrid donor are injected into newborn mice of one of the parental strains, though the recipients may become tolerant of homografts from the other parental strain.

In attempts to confer tolerance without the intervention of runt disease, leucocyte concentrates prepared from whole blood and suspensions of bone marrow cells were investigated. Contrary to expectation, since the majority of blood leucocytes in normal animals are thought to be expendable end-products incapable of further proliferation, it was found that suspensions of these cells are just as potent as spleen cells in causing runt disease. These results strongly suggest that at least one type of blood leucocyte is immunologically competent and capable of proliferation. Bone marrow cells, on the other hand, although they conferred tolerance very satisfactorily, rarely killed animals even when they were employed with strain combinations which would have invariably been fatal had splenic or lymph node cells been used. This finding is entirely consistent with the fact that marrow, unlike spleen, contains relatively little lymphoid tissue.

Quite independently, a phenomenon essentially similar to runt disease was

discovered in chickens by Simonsen, who had deliberately set out to put his original hypothesis about graft-versus-host reactions on a sound experimental basis. He found that the intravenous inoculation of embryonic chicks with splenic cells from an unrelated adult donor caused a fairly prompt enlargement of the host's spleen and liver, with distinctive pathological lesions in these and other organs, accompanied by an acute hemolytic anemia. The disease usually killed the hosts within a week or two of hatching. Careful histological studies strongly suggested that the affected organs of these animals had undergone varying degrees of replacement of their normal cell populations with proliferating lymphoid cells of donor origin. In the bone marrow, for example, the blood-forming cells were almost entirely replaced by lymphoid cells, and it was presumed that the native cell population had been destroyed immunologically. Simonsen also found that adult whole blood or the leucocytes isolated from it produced splenic enlargement on inoculation into embryos. This spleen-enlarging principle was serially propagated from 3-day old chicks to 18-day embryos and so on, for nine consecutive passages. Here, then, is unequivocal evidence that the inoculated cells must proliferate in their new hosts, presumably in response to the antigenic stimulus. Furthermore, as with the mice, the blood of adult chickens clearly contains immunologically competent cells. The fact that cells from very young donors did not affect their hosts was to be expected, on account of the immaturity of the immunologically competent cells. Indeed, the latter probably became tolerant of their hosts!

It had previously been established by other workers that experimental or natural parabiotic union between avian or mammalian *embryos* permitting a mutual exchange or cross transfusion of blood leads to the production of animals which are cellular chimeras and therefore are tolerant of subsequent grafts of tissues interchanged between them, but are perfectly normal in other respects—that is, there are no symptoms of runt disease.

In subsequent experiments Simonsen and Cock obtained even more compelling evidence that the splenomegaly and other lesions in the young chicks were the outcome of their cellular homografts reacting against them. Using inbred strains of chickens, Simonsen found that blood from one parental strain caused enlargement of spleens and livers on inoculation into newly hatched F_1 hybrid individuals, whereas adult hybrid blood inoculated into hybrid or parental strain hatchlings was without significant effect, as one would expect *ex hypothesi*. It may be emphasized that in both Billingham and Brent's work and in Simonsen's, care was taken to eliminate any possibility that "runt disease," or its equivalent in chickens, was caused by pathogenic organisms accidentally introduced along with the cells into immature and immunologically defenseless hosts. The disease is unequivocally immunological in origin, and the reacting cells are those of the graft.

It is interesting to recall that the striking splenomegaly that almost invariably follows the transplantation of adult homologous splenic tissue, and not infrequently grafts of other adult tissues, to the chorioallantoic membrane of the embryonic chick has been repeatedly observed for more than 40 years and accounted for by several ingenious hypotheses. Final solution of this problem was not possible until the recent development of the concept of graft-versus-host reactions. The solution depended also on an appreciation of the surprising mobility of apparently fixed lymphoid cells, and of their uncanny power of taking up residence among cells of their own kith and kin and turning upon their new neighbors.

Indeed, with appropriate controls, splenomegaly in the chick embryo furnishes a valid test for the presence of immunologically competent cells in grafts of homologous tissues from adult donors. For example, this test has revealed that adult chickens' skin, carefully perfused to remove all residual blood cells, still retains the spleen-enlarging property—hence must contain immunologically competent cells.

Evidence of the reaction of inocula containing immunologically competent cells against homologous embryonic or very young hosts has now been obtained in other species, including rats, hamsters, and rabbits; preliminary experiments suggest that the phenomenon occurs in salamanders too. The disease may also appear when donor and recipient belong to *different* species, as when the donor is an adult turkey and the recipient a chick embryo. In the reaction to heterografts, as in the normal homograft reaction, the grafted lymphoid cells appear to produce antibodies which may coat the red cells of the host, but there is no evidence that the antibodies are responsible for runt disease. A likely contributory factor to the deaths of the "runts" is probably their gross deficit of lymphoid tissue, which renders them highly susceptible to infection, for example, from pathogens present in their own intestines.

Fig. 4. Two 2-month old "A" strain mice which were injected at birth with C3H strain spleen cells. The smaller animal is suffering from chronic runt disease and weighs only 6 gm. Note the characteristic scruffy condition of its fur. Its brother weighs 22 gm and is perfectly healthy.

Delayed Deaths in Radiation Chimeras

The red blood cell forming and lymphoid tissues are particularly susceptible to ionizing radiations so that, at least in some species, and particularly in the mouse, it is possible to give a dosage of x-irradiation which is sufficient to destroy these two tissues, but does very little damage to the remainder. Of course, this treatment is normally fatal within a few days. However, if the irradiated mice are promptly given an intravenous injection of living cells from the blood-forming tissues of other mice—adult bone marrow or infant spleen—they will recover from the radiation syndrome.

Independent investigations, employing a variety of techniques, have shown that the protection afforded by the inoculated cells depends upon their migration to anatomically appropriate places, where they recolonize the depleted "frameworks" of the marrow spaces and lymphoid tissues and thus restore function. If the inoculated cells come from a genetically similar or isologous donor, the host may expect to live quite happily on its borrowed marrow for a very long time. If, however, donor and recipient belong to different strains the loan may be less satisfactory; deaths of the resultant *homologous chimeras* may occur within a matter of a few weeks or a month or two. Where protection is afforded by cells of *heterologous* origin—for example, rat to mouse—the life expectancy may be even shorter. These "delayed deaths" are attributed to a syndrome variously described as secondary radiation sickness, homologous disease, or wasting disease. The symptoms closely resemble those of runt disease: usually loss of weight, poor condition of the fur, diarrhea, and involution of lymphoid tissue.

Although all authorities are in agreement that this disease is immunological in origin, some division of opinion still prevails as to whether it is due to a reaction on the part of some of the grafted cells against the host, as Trentin first suggested, or to a gradual recovery of the host's *own* lymphoid cells, through the proliferation of a few survivors, and the immunological destruction or rejection by these host cells of the borrowed hematopoietic or blood cell forming tissue upon which survival of the animal depended. The general conclusion to be drawn from numerous experiments employing the same principles as those used in analyzing runt disease is that the delayed deaths following potentially lethal irradiation are a consequence of the cellular homografts reacting against their hosts. To mention only two of the many important pieces of evidence which support this conclusion: delayed deaths may be avoided by the use of cells from adult F_1 hybrid donors or cells from fetal donors. With lower dosages of irradiation the host is more likely to recover its own immunological defense mechanism so that the reaction of host against the cellular homograft becomes the predominating cause of death. There is, in fact, no reason why attacks from both directions cannot take place concomitantly if lymphoid cells of both donor and recipient types are present. The fact that homologous bone marrow inoculated into newborn mice induces immunological tolerance with only subclinical manifestations of runt disease, whereas homologous marrow inoculated into adult irradiated mice may cause a high proportion of delayed deaths (even with the same donor-recipient combination) is not necessarily paradoxical.

Although in an immunological sense the two situations are comparable—the hosts in both situations being immunologically defenseless—in an anatomical sense there are several important differences. Thus, in the irradiated animal the host's marrow and lymphoid tissues have been destroyed, making plenty of room for the small proportion of immunologically competent ingredients among the donor's marrow cells to establish themselves and build up a population large enough to cause immunological damage; in the newborn animal the limited sites available are already colonized so that there is less opportunity for insurgent cells to develop in sufficient numbers to do serious harm.

"Runt" or "Homologous" Disease in Genetically Tolerant Hosts

There is one immunogenetic situation which should give a graft every opportunity of reacting against its adult host yet require no pretreatment or conditioning of the latter. This obtains when cells from one parental strain are introduced into an F_1 hybrid (see previous section on genetic determination of transplantation antigens).

In some strain combinations, very young hybrid mice inoculated with parental strain cells are highly susceptible to acute runt disease but gradually become resistant; inoculations given more than about two weeks after birth are apparently harmless. Similar results have been obtained with hybrid chickens. In other mouse strain combinations, however, the adult hybrid mice do retain their susceptibility. How is this loss of susceptibility to be explained? It seems reasonable to suppose that the actual dosage of the cellular homograft and the "power" of the antigenic stimulus it receives from the host are important. The fact that sublethal dosages of irradiation increase the vulnerability of adult hybrids hints at another factor: insidious competition of the inoculated cells with the native and established cells for *lebensraum* before they can express their Quisling-like properties. Other things being equal, one might expect adult lymphoid cells to be at some advantage in competing with their homologues in immature hosts, but when recipient as well as donor is adult the situation may well be less favorable for the cells of the latter to gain lodgment unless they have been aided by a little site-clearing by prior sublethal irradiation. Moreover, hybrid cells may, like hybrid animals, possess a "vigor" which exceeds that of the parental strain cells.

One important question still to be resolved concerns the activity or fate of immunologically competent cells in those immunologically tolerant mice, radiation chimeras and F_1 individuals which do not succumb to graft-versus-host reactions. Unquestionably, many of these cells survive for very long periods, if not for the remainder of their host's lives. Do they maintain a chronic though virtually asymptomatic attack on their hosts—like the long-drawn-out course of some autoimmune diseases in which individuals react against some of their own specialized body ingredients?

Parabiosis Intoxication

Surgical parabiosis is, in effect, the grafting of two animals together, and has long formed part of the armamentarium of the endocrinologist. With parabiotic unions between members of the same species, usually rats or mice, a distinctive syndrome, commonly referred to as *parabiosis intoxication*, has long been recognized. Usually one parabiont loses weight and dies within a week or two after union, whereas its

partner appears unaffected—although sometimes both members may die. This disease has not been made the subject of systematic investigation, but there are strong indications that it is the outcome of an immunological incompatibility between the parabionts. For example, littermate rats are less susceptible to it than nonlittermate rats, and inbred mice may be parabiosed with impunity. Also consistent with this interpretation are reports of involution of the lymphoid tissues and spleens of the smaller animals and of a hyperplasia of these tissues in the larger animals. So far as it goes, all the evidence suggests that there is a striking similarity between parabiosis intoxication and homologous or runt disease.

Pregnancy in mammals may also be regarded as a form of parabiosis or homotransplantation. However, the complete separation of the fetal from the maternal blood circulations is generally held to be the most important factor in preserving these animals from immunological extinction. However, in man, hemolytic disease of the newborn is an unpleasant reminder that this barrier is not completely infallible. Hemolytic disease is usually held to be brought about by the accidental entry of "foreign" fetal cells into the mother, where they elicit the formation of antibodies. These then pass back across the placenta into the fetal circulation. However, there is an alternative mechanism which may be worth bearing in mind, now that it has been shown from the experiments on runt disease that adult blood contains immunologically competent cells. Hemolytic disease may be caused by the entry of maternal *leucocytes* into the fetus, where they become established as cellular homografts and so react against the host from *within*. Although there are cogent reasons why this explanation cannot be applicable to all cases of hemolytic disease of the newborn, it would certainly account for the small proportion of recorded cases in which no evidence of sensitization was forthcoming from examination of the mother's blood.

Conclusion

Runt disease in small rodents or chick embryos provides one of the simplest diagnostic tests for immunologic competence of inoculated adult cells. For example, it has shown unequivocally that the thymus contains such cells, a finding paralleled by the fact that homologous disease may follow the inoculation of parental thymocytes into sublethally irradiated F_1 hybrid hosts. Furthermore, experiments currently in progress show that the median survival time of newborn mice inoculated with a constant dosage of cells obtained from different types of lymphoid tissue can be employed as a quantitative measure of their relative immunological efficacy. This test system is already being used in several laboratories to find out which of the types of leucocytes is responsible for the immunological reactivity of peripheral blood. The two principal candidates appear to be the so-called small and large lymphocytes, of which the former is by far the more abundant.

Of clinical interest is the possible use of body "spare parts" if the problem of homograft survival should be solved. Before the widespread utilization of clinical spare parts could be safely undertaken, it would be necessary to evaluate carefully the possible importance of graft-versus-host reactions. Could a kidney homograft, for example, conceivably damage its host by virtue of the small amount of lymphoid tissue it contains? The question is clearly irrelevant in the case of some tissues, such as skin, which lack lymphoid-type cells. The risk of incurring "homologous disease" in man has already been justifiably undertaken. For example, reports have recently appeared in the lay press of the apparently successful treatment of five patients who had accidently received high dosages of irradiation by giving them infusions of adult homologous marrow. Attempts are also being made to employ total body irradiation in the treatment of leukemia, the widespread damage to the patient's blood-forming tissues being made good by infusions of homologous marrow cells. A well-recognized complication here is the fact that functional lymphoid tissue is essential for the individual to protect himself against pathogens. As the experiments already described in this article have shown, one way in which this risk can be eliminated is to employ immature tissues from fetal donors, so that the transplanted lymphoid-type cells will become tolerant of their host.

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Automatic Linkage of Vital Records

Computers can be used to extract "follow-up" statistics of families from files of routine records.

H. B. Newcombe, J. M. Kennedy, S. J. Axford, A. P. James

The term *record linkage* has been used to indicate the bringing together of two or more separately recorded pieces of information concerning a particular individual or family (*1*). Defined in this broad manner, it includes almost any use of a file of records to determine what has subsequently happened to people about whom one has some prior information.

The various facts concerning an individual which in any modern society are recorded routinely would, if brought together, form an extensively documented history of his life. In theory at least, an understanding might be derived from such collective histories concerning many of the factors which operate to influence the welfare of human populations, factors about which we are at present almost entirely in ignorance. Of course, much of the recorded information is in a relatively inaccessible form; but, even when circumstances have been most favorable, as in the registrations of births, deaths, and marriages, and in the census, there has been little recognition of the special value of the records as a source of statistics when they are brought together so as to relate the successive events in the lives of particular individuals and families. The chief reason for this lies in the high cost of searching manually for large numbers of single documents among vast accumulations of files. It is obvious that the searching could be mechanized, but as yet there has been no clear demonstration that machines can carry out the record linkages rapidly enough, cheaply enough, and with sufficient accuracy to make this practicable.

The need for various follow-up studies such as might be carried out with the aid of record linkage have been discussed in detail elsewhere (*1*, *2*), and there are numerous examples of important surveys which could be greatly extended in scope if existing record files were more readily linkable (*3*). Our special interest in the techniques of record linkage relates to their possible use (i) for keeping track of large groups of individuals who have been exposed to low levels of radiation, in order to determine the causes of their eventual deaths (see *4*, chap. 8, para. 48; *5*), and (ii) for assessing the relative importance of repeated natural mutations on the one hand, and of fertility differentials on the other, in maintaining the frequency of genetic defects in human populations (see *4*, chap. 6, para. 36*c*).

Our own studies (*6*) were started as part of a plan to look for possible differentials of family fertility in relation to the presence or absence of hereditary disease (through the use of vital records and a register of handicapped children). The first step has been the development of a method for linking birth records to marriage records automatically with a Datatron 205 computer. For this purpose use has been made of the records of births which occurred in the Canadian province of British Columbia during the year 1955 (34,138 births) and of the marriages which took place in the same province over the 10-year period 1946-55 (114,471 marriages). Fortunately, these records were already in punch-card form as a part of Canada's National Index, and from them could be extracted most of the necessary information on names and other identifying particulars. An intensive study of the various sources of error in the automatic-linkage procedure has now been carried out on approximately one-fifth of these files.

Technical Problems

One of the chief difficulties arises from the unreliability of the identifying information contained in successive records which have to do with the same individual or married pair. The spellings of the surnames may be altered, the first Christian name on one record may become the second on another, and the birthplaces and ages may not be correctly stated. Much of the design effort must be directed toward ensuring that records can be linked in spite of such discrepancies, which in our files occurred with frequencies of about 10 percent of all record linkages involving live births and 25 percent of all linkages involving stillbirths.

A second problem relates to ambiguous linkage, in which it is uncertain whether or not a birth has arisen out of a particular marriage, or where there are two or more marriages any one of which might be that of the parents. These problems tend to occur when the husband's surname and the wife's maiden name are both common in the region studied, but they can also be associated with rarer family names, as in the marriage of two brothers to two sisters, and in certain racial minority groups. The difficulty increases with the size of the population under study.

At first sight these considerations might seem to preclude any extensive use of automatic record linkage as a source of statistics, since it is not at all obvious that the rules of judgment as exercised by a human being can be adapted to machine use. Also, partially mechanized record-linkage operations have proved laborious in the past (*7*).

Nevertheless, satisfactory procedures were eventually developed. These began with a series of small-scale attempts to link records visually, and thus to gain insight into the causes of any failures. The first of these studies was carried out at the Bureau of Statistics by one of us (S.J.A.) and made use of one of the standard phonetic name-coding systems to reduce the undesirable consequences of spelling discrepancies in linking records of sibling stillbirths. The gradual evolution of the method since that time has served to make it evident that further refinements can undoubted-

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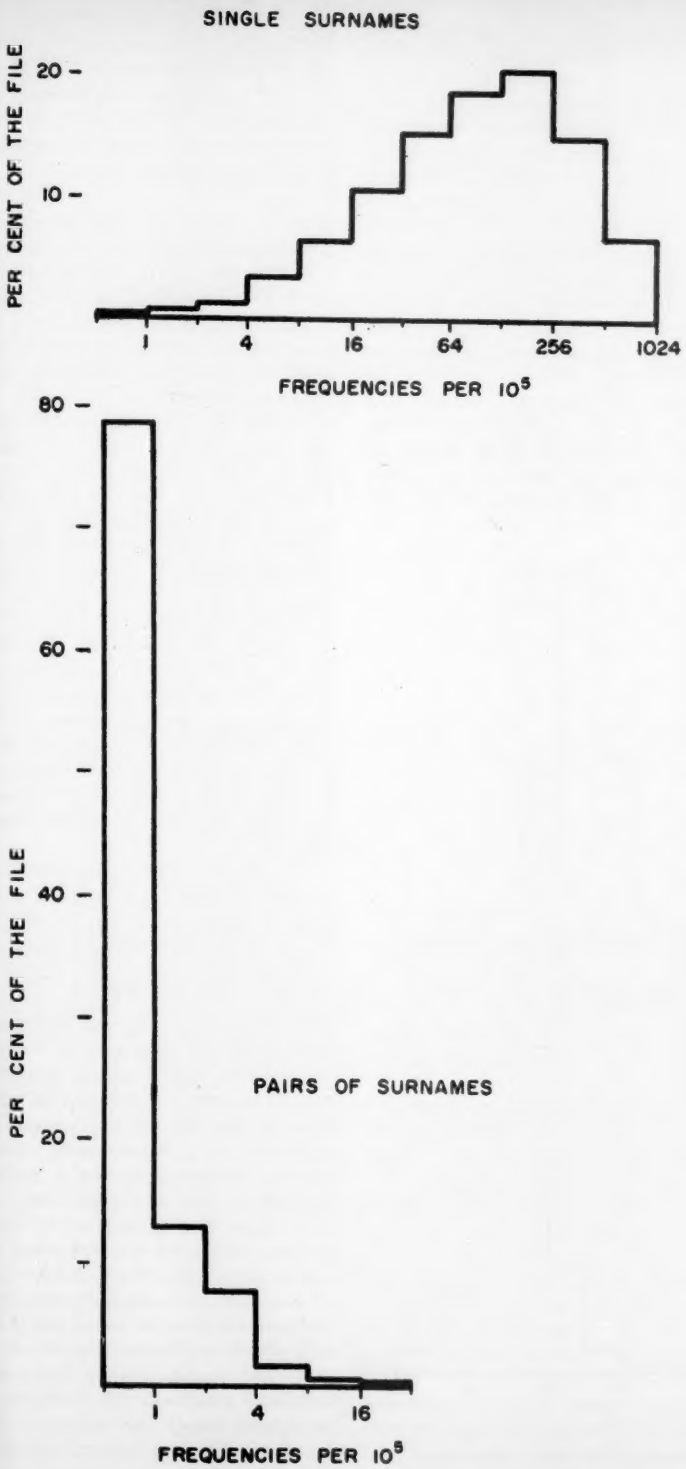

Fig. 1. (Top) Frequency distribution of brides' maiden names, in Soundex coded form, from records of 114,471 marriages in British Columbia for 1946–55. (Bottom) Frequency distribution of family-name pairs for married couples, in Soundex coded form, from the same records. Two East Indian names, of which one is customarily passed from mother to daughter and the other from father to son, were omitted. These occurred together in the same combination in approximately 100 marriages.

ly be developed and that no limit to the possible reliability of the linkages is yet in sight.

Methods

Of primary interest was the development of a procedure which would be fully automatic and free from piecemeal operations which might later limit the usefulness of the approach. This aim was achieved, chiefly because the use of a computer made it possible to compare each birth record in turn with all of the marriage records in appropriate sections of the marriage file. Since groups of marriages were sometimes scanned a number of times, it is apparent that this operation could not have been carried out with conventional card-handling equipment. Thus, without the computer, a visual search through printed lists would have been required to achieve some of the linkages.

To reduce the number of marriage records with which the computer must compare a birth record, it was decided to make use of both the husband's surname and the wife's maiden name, these being present on both the marriage and the birth cards. The surnames were first reduced to phonetic codes, consisting in each case of the first letter of the name followed by three numeric digits and known as the Russell Soundex Code (*8*), the computer being used for the coding operation. The codes served two purposes: They were designed to remain unchanged with many of the common spelling variations and in the present application were thus expected to bring together linkable records which would have been widely separated if arranged in a strictly alphabetic sequence. The coding also simplified the subsequent use of the Datatron computer, which is essentially a mathematical instrument and works more readily with numbers than it does with letters.

The extent to which two surnames are more efficient than one for identifying a family group has probably not been generally recognized. Thus, of the various brides' maiden names encountered in the marriage file, more than half recurred (in their coded forms) with frequencies in the range from 64 up to 1024 per 10^5. In contrast to this, nearly 80 percent of the pairs of family names (in their coded forms) were unique; that is, they occurred only once in our file in that particular combination, and extremely few had frequencies exceeding 4 per 10^5 (see Fig. 1). This

meant that we could mechanically compare each birth for the entire year with all of the marriages, using the same pair of surname codes, and that only rarely would the number of code matchings exceed one or two per birth.

To enable the computer to decide whether or not a birth and a marriage relate to the same married pair, use must be made of other identifying particulars. We relied chiefly on six items: the full alphabetic family names of the husband and wife (limited to nine letters each), their provinces or countries of birth (each coded as a two-digit number), and their first initials. In addition, the ages of the married pair were available on our cards for all of the birth records and for about half of the marriage records (that is, for marriages in the period 1951-56); the second initials were present in the case of the birth file; and the name of the city or place of the event (restricted to six letters) was available throughout both files.

As mentioned earlier, no one piece of information was entirely reliable. Usually it was obvious on inspection that the two events did, or did not, relate to the same married pair, but occasionally the decision was difficult. For this reason the computer had to calculate a probability that the couples were the same, or were different. The operation was performed automatically when the files were first matched.

The principle on which such a probability was based is fairly simple. If, for example, the province or country of birth of both the husband and wife agree on the two records, these facts may influence somewhat our belief that these records relate to the same married pair. Of course, the weight which one attaches to the information will be small if both have been born in the home province of British Columbia, but it will be large if they happen to have been born in, let us say, Switzerland and New Zealand, respectively. To give this a mathematical form it is necessary to know the frequencies for the various birthplaces of brides and grooms, and these can be determined quite readily either from published statistics or from the files themselves.

Similar reasoning can be applied to any item of identifying information, and to both agreements and disagreements. In order that the probabilities may be added together they must be converted to logarithms, and it is conventional practice in information theory to use logarithms to the base 2 of the probabilities expressed in the form of the "odds," for or against. The units are known as "binits." Thus, if the odds were 16 to 1 in favor of a genuine linkage, this would be represented as plus 4 binits, and odds of 16 to 1 against would be minus 4 binits. It is convenient to remember that a value of 10 binits is equivalent to odds of approximately 1000 to 1.

For present purposes, the probability or odds associated with a given agreement or disagreement may be obtained in binit units from the expression:

$$\log_2 p_L - \log_2 p_F \qquad (1)$$

where p_L and p_F are the frequencies with which the agreement or disagreement occurs, respectively, in the linked pairs of records and in pairs which have been brought together by accident. The expression will have a positive value in the case of agreement and a negative value in the case of disagreement.

As applied to agreements of initials and birthplaces, the expression can usually be simplified without any great loss of accuracy, since the particular letter or place should agree in the linked records almost as often as it appears in the individual records, and the chance of a fortuitous agreement will in most cases be approximately the square of this frequency. By substitution, expression 1 thus becomes:

$$\log_2 p_R - \log_2 (p_R)^2 = -\log_2 p_R \qquad (2)$$

where p_R is the frequency of the particular initial or birthplace in the individual records.

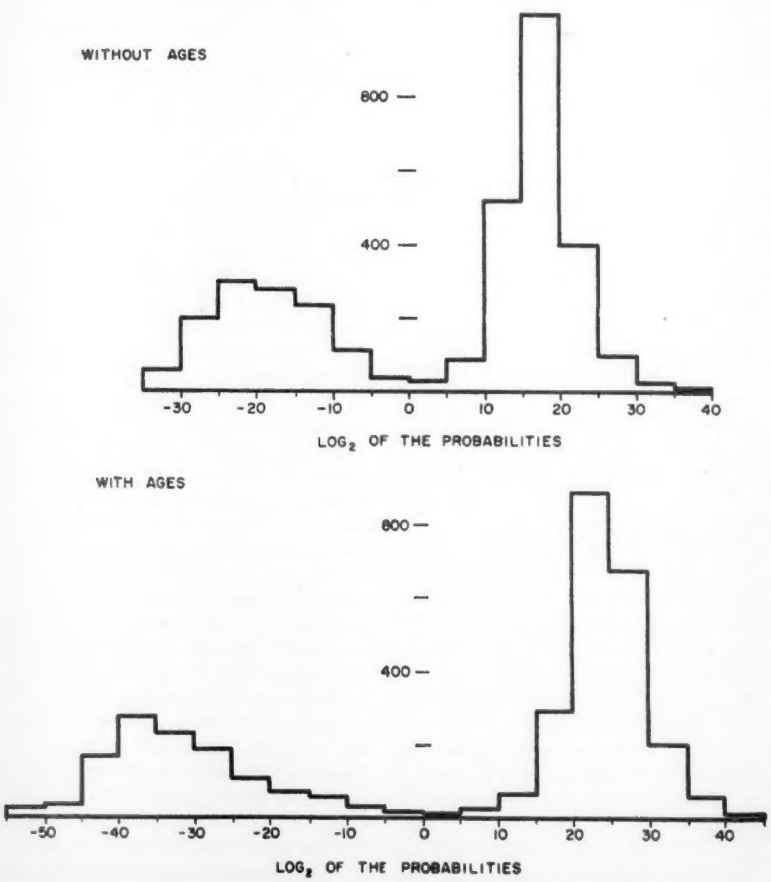

Fig. 2. (Top) Frequency distribution of the probabilities (in binits) obtained on comparing birth and marriage records having identical Soundex code pairs (calculated without using ages), based on records contained in the first fifth of the birth and marriage files (husband's surname beginning with *A*, *B*, or *C*). For this comparison only legitimate live births and marriages recorded in 1951-55 (a period for which ages are available) were considered. There were 2174 cases of genuine linkage and 1232 cases of accidental Soundex agreement. (Bottom) Same as above, except that the ages were used in calculating the probabilities.

The approach also lends itself to comparisons of the ages as stated on the two records, the lapse of time between the two events, and whether a discrepancy, if present, is slight or large, being taken into account. Even such an unlikely item as the place of the event can be used; if the marriage and the birth occurred in different places the fact carries little weight, but if they occurred in the same place (provided it was not the largest city in the province) the fact is important.

The items from which the probabilities were calculated in our study were the two alphabetic surnames, the two birthplaces, the two first initials, the two ages (where these were given on the cards), and the place of the event. For possible future use the computer also compared the birth order with the apparent duration of the marriage at the time of the birth, and wherever a first initial failed to agree, the computer looked for agreement between the first initial on the marriage record and the corresponding second initial on the birth record.

This sort of treatment can be adapted to linking almost any types of records where the information in common is sufficient for the purpose. Although tables of probabilities (in binits) containing over 300 items were used in the present study, they did not exhaust the capacity of the computer's memory unit. The limiting factor is the discriminating power inherent in the information supplied, and it is apparent that additional items of information can be of use even where they are of limited reliability.

The extent to which ages, for example, enable the computer to separate the genuine linkages from the fortuitous Soundex agreements can be seen from the data of Fig. 2. In this case, the number of record comparisons falling in the region from minus 10 to plus 10 binits, where the degree of certainty is less than 1000 to 1, is reduced by a factor of 3 when use is made of the additional information.

Reliability of the Linkages

Studies of the accuracy of the present computer-handling procedures indicate that about 98.3 percent of the potential linkages are detected in the existing record files, and that contamination with spurious linkages is 0.7 percent [see (9)]. This degree of accuracy is considered adequate for the statistical studies which have been planned, since the loss of such a small amount of data cannot in itself constitute a source of bias. Further, both the losses and the contaminations can be detected in the majority of cases by means of a subsequent check on the continuity of birth orders within families.

Variations in the spelling of the family names occur in about 4 to 5 percent of all linkages, but the losses from this source are reduced by the use of the phonetic codings to approximately a third of that value (see Table 1). The detection of such losses was accomplished by the simple expedient of resorting the files in a sequence which ignored the suspect code but trusted other identifying items, the files then being listed and examined visually. This operation could have been performed by the computer, and since the six main identifying items all agree in about 90 percent of the linked pairs of records (see Table 2), two additional arrangements of the files, each of which ignored one of the two Soundex codes, would be sufficient to reduce losses of this kind from the present 1.6 percent to about 0.16 percent. For the projected statistical studies such a procedure would hardly be worth while, the computer time being the limiting factor. It might become of value for other purposes, however, as computer speeds increase, especially as it is customary for central registry offices to keep two separate listings of marriages for searching purposes, arranged under grooms' surnames and brides' maiden names, respectively.

Failure of the calculated probabilities to make a correct distinction contributed a few additional losses and a few spurious linkages. These were detected by comparing the full Christian names as given on the original registration forms wherever the calculated probability fell within the range from minus 10 to plus 10 binits. Where age was used in calculating the probabilities there were only one loss and four spurious linkages from this source in a sample of over 2000 linkages (see Table 3). Although this degree of accuracy is adequate for almost any purpose, to make a further reduction in the number of spurious linkages would not be difficult.

Table 1. Surname spelling discrepancies*.

Name	Number of linkages in sample	Total spelling discrepancies		Discrepancies affecting the phonetic codes	
		No.	Percentage	No.	Percentage
Husband's surname	3622	41	1.1	15	0.4
Wife's maiden name	3501	115	3.3	42	1.2
Combined			4.4		1.6

* Based on visual linkages of births with marriages. To detect spelling discrepancies in a random assortment of the family names of one partner, use was made of the parts of the files in which the family name of the spouse began with *A*, *B*, or *C*. Thus, the two samples of records each represented approximately 19 percent of the total files.

Table 2. Discrepancies in birthplaces and first initials*.

Category	Number of linkages in sample	Discrepancies	
		No.	Percentage
Birthplace of husband	2174	22	1.0
Birthplace of wife	2174	21	1.0
First initial of husband	2174	60	2.8
First initial of wife	2174	83	3.8
Total			8.6
Total, including surnames			11.4
Linkages having discrepancies in one or more of the six items			10.3

* Discrepancies in computer linkages of records contained in the first fifth of the birth and marriage files (husbands' surnames beginning with *A*, *B*, or *C*); only linkages of legitimate live births with marriages in the period 1951-56 (for which ages were available) were used. For the "total, including surnames," use was made of the data from Table 1.

Table 3. Losses and spurious linkages due to lack of sufficient identifying information, which occurred in the linkage reported in Table 2 (9).

Item	No. of linkages in sample	Losses		Spurious linkages	
		No.	Percentage	No.	Percentage
Age data used	2174	1	0.05	4	0.23
Age data not used	2174	5	0.2	26	1.2

The contamination with spurious linkages will tend, however, to vary in direct proportion to the size of the marriage file with which the births are compared. Thus, in any future studies of larger populations it might be desirable to make use of additional identifying information. Christian names (perhaps restricted to four letters each), the city of birth of the husband and of the wife, respectively (likewise restricted to a few letters), and the province and year of marriage (not shown at present on the birth registration form) would all be suitable data for this purpose. The last of these three groups of items, however, would be of special value in effectively reducing the size of the marriage file with which any one birth would have to be compared, and in this manner reducing the false linkages. Occasional inaccuracies in the additional information would not greatly alter its usefulness in view of the nature of the handling procedures.

It is doubtful whether the present accuracy of the procedure can be matched by that of conventional survey and interview techniques, and its potential accuracy is certainly much greater than that of conventional techniques.

Speed of Record Linkage

By far the largest part of the effort in this undertaking has gone into the preparation of the card files. This has included, in the case of the marriage cards, a mechanical reproduction of the information contained in the existing National Index marriage cards for brides and for grooms, respectively, on a single card of our own format. Likewise, a part of the contents of our birth cards was obtained by reproduction from existing National Index birth cards, but in this case the maiden name of the mother and a number of other items were then added from cards which had been especially key-punched for the purpose. The family names on all cards in both files were Soundex coded by means of the computer, and the files were sorted into a Soundex sequence by pairs of codes, and listed. For the purpose of the initial record-linkage study the part of the marriage file for married pairs in which the groom's surname began with *A*, *B*, or *C* (approximately one-fifth of the total file) was transferred to magnetic tape.

This done, the computer made the necessary birth-to-marriage comparisons when presented with the birth cards, matchings with respect to the pairs of name codes being achieved at a rate of approximately one comparison every 3 seconds. About half of these code agreements represented genuine linkages (*10*). (Subsequently the whole of the birth and marriage files were put on magnetic tape and linked automatically by the computer.)

The initial steps would be largely eliminated were the format of the cards which are prepared routinely designed with a view to their possible use for record-linkage purposes. Also, an improvement in the rate at which the computer makes the comparisons can be gained in later operations by limiting the longer computations to the relatively small number of comparisons where simpler tests are inadequate. Some other short cuts might well be effected in the program if it were used sufficiently to justify the time involved. Such improvements can be thought of as reducing the cost of record linkage, in which computer rentals may be a major item, and of increasing the ease with which statistics can be derived from the linkage process.

The use of a computer especially designed to handle alphabetic information would further reduce the time required for the linkages by virtue of this special design alone, and there are larger computers in which the basic logical steps are more rapid by an order of magnitude. Thus, the present rate of something like one linkage every 6 seconds might be increased perhaps 20- or 30-fold—that is, to 200 or 300 linkages per minute, with existing equipment.

It is difficult to guess to what extent these speeds will be exceeded in the next 10 years or so. However, circuits have been described in the literature in which the basic logical steps take much less time than those in any equipment at present on the market (*11*). Research with the more novel kinds of electrical switching devices, some of which are not only fast but extremely compact, may extend the present limit by at least another order of magnitude (*12*).

Well before such equipment becomes available, however, it should be possible to develop the data-processing methods by which record linkages are achieved to the point at which the extraction of a wide variety of family and follow-up statistics becomes practicable from any records which are in an accessible form.

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6. We are indebted to John H. Doughty for his encouragement and constructive criticism in the course of this work, to Robert J. Montgomery for making available facilities for the preparation of the marriage file, and to George Selby for his help in this initial operation. We would also like to thank Elizabeth Kinsey for collaborating in the preparation of the record files and in the analysis of the results, and Arden Okasaki for her work in programming the computer. Permission to use the vital records in this study was obtained through the Dominion Bureau of Statistics, from the Health Branch, Department of Health and Welfare, Province of British Columbia. The permission was conditional upon strict observance of the oath of secrecy respecting the nonstatistical information contained in the records.
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8. The rules of Soundex coding are as follows. (i) The first letter of a surname is uncoded and serves as the prefix letter. (ii) W and H are ignored completely. (iii) A, E, I, O, U, and Y are not coded but serve as separators (see v below). (iv) Other letters are coded as follows, until three digits have been used up (the remaining letters are ignored): B, F, P, V, coded 1; D, T, coded 3; L, coded 4; M, N, coded 5; R, coded 6; all other consonants (C, G, J, K, Q, S, X, Z), coded 2. (v) Exceptions are letters which follow letters having the same code, or prefix letters which would, if coded, have the same code. These are ignored in all cases unless a separator (see iii above) precedes them.
9. Since ages were available on only about half of the marriage cards, the average losses from this cause were 0.12 percent of all linkages, and the average spurious linkages were 0.7 percent. When these are added to the losses resulting from the Soundex discrepancies, as shown in Table 1, the total loss is 1.72 percent.
10. It is known that approximately 19 per cent of the surnames in the marriage file begin with A, B, or C, as determined from studies of the frequencies of brides' Soundex codes. Thus, of the 114,471 marriage records and 34,138 birth records, approximately 21,750 and 6500 records, respectively, were used in the initial linkage study. In all, 6375 comparisons (3484 with positive binit values and 2891 with negative) between birth records and marriage records having identical pairs of Soundex codes were made by the computer. Of these, 418 (20 positive and 398 negative) related to illegitimate births, 2549 (1285 positive and 1264 negative) related to legitimate births and to 1946-50 marriages, and 3408 (2179 positive and 1229 negative as determined by means of ages) related to legitimate births and to 1951-55 marriages. Since age records were available in the case of the 1951-55 marriages,

this latter group of 3408 comparisons was used for a detailed study of the reliability of the machine linkage process. (Revised tables of binit values were also derived from these comparisons.) Two of the 3408 comparison cards were removed because in each case one of the ages was missing. Of the remaining 3406 cards, 2174 represented genuine linkage (2173 positive cards plus one negative card) and 1232 represented accidental Soundex agreements (4 positive plus 1228 negative cards), as judged by comparisons of the full Christian names in all cases where the binit values fell within the range from minus 10 to plus 10. It will be noted that of the 6500 births of 1955 which were studied, 3484 (54 percent) were from marriages contracted in British Columbia during the 10-year period 1946-55. For a description of the manner in which visual record linkages (as distinct from computer linkages) were used to assess the losses due to spelling discrepancies, see footnote to Table 1.

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Genetics and the Hierarchy of Biological Sciences

Genetics is binding biology at all levels, from macromolecule to species, into a unified discipline.

Sewall Wright

"History shows that throughout the centuries . . . natural history constitutes the perennial rootstock or stolon of biologic science and that it retains this character because it satisfies some of our most fundamental and vital interests in organisms as living individuals more or less like ourselves. From time to time the stolon has produced special disciplines which have grown into great, flourishing complexes. . . . More recently another dear little bud, genetics, has come off, so promising, so self-conscious, but alas, so constricted at the base."

This quotation from William Morton Wheeler (*1*) expresses a common viewpoint of non-geneticists of Wheeler's time. There were even geneticists who saw little future in genetics, not because its field seemed trivial, but rather because they were so dazzled by the achievements of the first two decades of the century that they felt that there was little left for them to do. I recall a talk I had about that time with a prominent geneticist who had decided to go into a different field. "Genetics," he told me, "is a cow that has been milked."

There are two polar interests in biology. One is the fascination with the diversity of life which Dr. Wheeler so notably exemplified. I can testify to the enthusiasm which he could arouse by his lectures and the exhilaration which one felt during field trips conducted by him. At the other pole is the fascination with the interconnectedness of things. My thesis is that genetics has become the stolon, in a different sense from Wheeler's, which is most effectively binding the whole field of biology into a unified discipline that may yet rival the physical sciences.

Classification of the Biological Sciences

There are many ways in which one may classify the biological sciences. I will not pause on classification by utility—medicine and public health, the agricultural sciences, forestry, etc.—though genetics has much to contribute to these. Nor will I pause on classification by kind of organism—mammalogy, ornithology, and so on down. Genetics cuts across them all. Branches of science also tend to grow out of techniques. Genetics centers in the techniques of breeding organisms. Breeding has turned out to be a remarkably penetrating technique, and one capable of joining forces with other techniques of the most diverse sorts in fruitful ways. For our purpose, however, the most instructive classification is by principles (*2*).

Biology deals with a hierarchy of entities. The primary subdivision of biology is perhaps best made according to level in this hierarchy. Biology began with *individuals*, Wheeler's natural history. It worked down through *organs* and *tissues*, categories that cut across each other, to the *cell*, as the almost universal unit of structure and function, and one that behaves in significant ways as an autonomous organism on its own account. For many years, biologists thought of the cell as the ultimate unit of life, composed of ordinary non-living molecules but organized in a way that conveys the properties of life. The geneticist has added a new level, the *gene*, an entity present in large numbers in the cell, controlling the specific properties of the cell but itself autonomous with respect to its specificity.

Moving in the other direction from the individual, towards larger units, we may proceed through local interbreeding populations (*demes*) to the *species*, an entity that persists with certain properties in spite of frequent complete replacement of all of its constituents. The integrating principle of the species is biparental reproduction. Cutting across this, somewhat as organs cut across tissues, are *ecologic systems* which maintain more or less constant patterns by means of self-regulatory interactions among the local representatives of many species. Finally, we have the entire *fauna* and *flora* of the world as a single, interconnected, more or less persistent system, a vast symplasm, to use Wheeler's word.

At all levels there are problems: (i) of describing the persistent entities and (ii) of accounting for their persistence; (iii) of describing and (iv) accounting

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This article is his presidential address before the 10th International Congress of Genetics, on 20 August 1958, in Montreal, Canada. It is reprinted from Volume I of the *Proceedings* of the X International Congress of Genetics by permission of the General Organizing Committee of the Congress.

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for the orderly second-order changes by which biologic entities characteristically develop; and finally (v) of describing and interpreting the processes by which the entities at the lower levels multiply (Table 1).

Genetics at the Level of the Individual

Genetics began at the level of the individual with curiosity about the similarities and differences among individuals related by descent. Rapid exploration in many species of animals and plants, once the key was given, led to the generalization that the rules of inheritance are everywhere much the same. Genetics, thereafter, settled down largely to the intensive study of a few especially favorable higher organisms: for example, *Drosophila,* the silkworm, the mouse, and the domestic fowl among animals; the garden and sweet pea, maize, antirrhinum, cotton, and tobacco among plants.

In the last few years, however, our concepts have been greatly enriched by a tremendous development of the genetics of microorganisms, some of which could not even be crossed until recently: *Paramecium, Neurospora, Aspergillus,* yeast, various bacteria and their phages, and others.

I believe that the list of organisms that can contribute significantly is not yet exhausted. Many of those that have been studied less extensively have contributed interesting but often overlooked phenomena, not encountered in the major objects of study. I am thinking of such things as the very odd genetics found by Metz in *Sciara* (*3*). There is still a tremendous field of comparative genetics that will reward pioneers.

Genetics and Cytology

Mendel's laws of heredity and a knowledge of the behavior of the chromosomes in mitosis and meiosis first entered the same minds very shortly after 1900. The firm establishment of the chromosome theory of heredity was the great achievement of the next two decades. Cytology became the first major branch of biology with which genetics became welded, to form the field of cytogenetics.

In the middle period of our history since 1900, the discovery of modes of inducing gene and chromosome mutations, and the demonstration of one-to-one relations between details of the linkage maps and those of the salivary chromosomes of *Drosophila melanogaster,* were among the outstanding events at this cytogenetic level.

Recently, the electron microscope has provided means for carrying the analysis of chromosomes much farther. The threadlike leptotene chromosomes as seen with the highest-powered light microscope, readily suggested the notion of single giant molecules. The tropical jungle of twisting lianas which the electron microscopists present as the real appearance of these same objects reminds us that the chromosome is separated from even macromolecules by several orders of magnitude (*4, 5*). The Watson-Crick molecule of DNA is some 20 A in diameter. The numerous chromosome fibrils, revealed in electronmicrographs, seem to be some ten times this in diameter, and the finest threads distinguishable under the light microscope are some ten times again as thick. The relation between a DNA molecule and a leptotene chromosome is thus somewhat like that between a wire 1 mm thick and a cable some 10 cm thick.

There are obviously still plenty of problems in cytogenetics. With the new techniques, including radioactive markers (*6, 7*), as well as the electron microscope, there are exciting prospects.

The Gene: Earlier Ideas

We come now to the level in the biological hierarchy that is the distinctive contribution of genetics, the gene. It was easy enough when I first used this two-dimensional classification of the biological sciences some forty years ago to subdivide the bottom row, the theory of the gene, into formal categories, similar to those at the higher levels, but these had little substance, and it was hard to imagine that they ever would have much. The recent period of our history has, however, been characterized especially by giving substance to just these aspects of genetics. On the other hand, the disconcerting question whether there is any such thing as a gene has been raised by Goldschmidt (*8*), a very great geneticist, whose provocative points of view we are going to miss badly. I wish to devote most of my time to questions at this basic level.

For his dominant and recessive units Mendel used the word *Merkmal,* which Bateson translated into English as "character." The term *unit character* seemed to imply a return to the discredited preformation theory of heredity and doubtless contributed to the suspicion of genetics felt by other biologists. It was, however, rapidly established that the heredity of characters tended to split up into many independently segregating pairs. It came to be recognized that *unit factor* was a better term than *unit character,* and, a little later, Johannsen's term *gene* was welcomed as a distinctive one for the basic unit of heredity.

There has remained some ambiguity in the frequent use of this term for both the common substrate of alternative units and a particular one of these. I will use the later term, *locus,* for the substrate and restrict *gene* to a particular representative of a locus, considered by itself.

The fact that analysis seemed to indicate the existence of dominant and recessive pairs led to the presence and absence hypothesis of Bateson and Punnett. As early as 1904, however, Cuénot (*9*), on analyzing the heredity of coat color of the mouse, had clearly demonstrated a set of multiple alternatives, as well as several independent pairs, and it came to be recognized by 1915 that multiple sets were not uncommon.

It was natural at first to extend the presence and absence theory to multiple alleles by postulating differences in quantity of the gene. It was soon realized, however, that qualitative differences in the gene and its primary product, conjectured to be an enzyme, might register physiologically as mere quantitative variations of characters. Then it turned out that pleiotropic effects of multiple alleles did not always fall in the same order. I strained myself considerably at about this time (*10*) trying to account for lack of parallelism in the effects of four (later five) alleles at the albino locus of the guinea pig on various colors of coat and eye, on the basis of differences in thresholds and competition or its absence. In the end (*11*) it could only be concluded that the five alleles determined five qualitatively different tyrosinases, even though different thresholds and competition effects were certainly present.

The patterns of differential effect within multiple sets of alleles have indeed turned out to be extraordinarily diverse, even though one can usually trace a thread of physiological similarity of some sort. We find complementary (*12*) as well as noncomplementary recessive alleles of wild type, differences in localization of patterns (*13, 14*), differences

in order of effect on different characters that lead in extreme cases to alleles that seem to have no more in common in their differences from type than random nonalleles (such as some of the alleles at the dumpy and spineless loci of *Drosophila melanogaster* (*15*). There are series in which many antigenic properties occur in all possible relations among the alleles (*16*): incompatibility, positive or negative correlation, and asymmetrical dependence, as well as apparent independence. Finally we have such curious manifestations of qualitative diversity as the self-incompatibility series of many plants (*17*) and Whiting's (*18*) nine sex-determining alleles of *Habrobracon* (any heterozygote: female; any homozygote or hemizygote: male).

It should be noted, in view of the current confusion in the use of the term *allelic*, that I am using it to describe a genetic relation, not a physiologic one, in conformity with Bateson's (*19*) definition of *allelomorphic* (of which *allelic* is a contraction), "alternative to each other in the constitution of the gametes." I am using allele as a representative of a locus, considered in relation to another, irrespective of physiological relations.

Conceptions of the locus as a physical entity were, of course, guided by cytologic observations. The early demonstration of the persistence of individualized chromomeres and their pairing in synapsis (*20*), Belling's demonstration (*21*) of as many as two thousand such particles in favorable materials, culminating in the demonstration of some five thousand identifiable bands in the salivary chromosomes of *Drosophila* and the location of particular loci in or near such bands by Painter (*22*) and Bridges (*23*), led to general acceptance of the particulate nature of loci. Estimates of average size of loci in the millions in terms of molecular weight, by Morgan (*24*) and Muller (*25*), seemed to give adequate scope for patterns capable of mutating at hundreds of different sites within a single locus and thus an adequate basis for the complexity of the observed allelic series.

Chemical Basis of Heredity

Perhaps the most revolutionary achievement of the recent period of our history has involved the chemical basis of heredity. It had been known since Miescher's work in the 1870's that chromosomes (of fish sperm) are largely composed of protein and nucleic acid. Until rather recently, nucleic acid seemed ruled out as the site of specificity by its supposedly monotonous tetranucleotide structure. Most geneticists up to the middle 1940's assumed that there was little choice but to suppose that specificity resided in a pattern of successive amino acids. Then came the discovery that the pneumococcus transforming principle, acting like a free gene, was probably pure DNA (*26*), and the recognition by biochemists that there was after all an adequate basis for specificity in the sequence of nucleotides in chains of indefinitely great length. The demonstration of constancy of DNA per chromosome set (*27*) added to the confidence in its genetic significance.

There was a transition period when the conjecture of a reciprocal relation between protein and DNA, each imposing specificity in synthesis of the other (*28*), seemed most attractive, but soon Watson and Crick (*29*) gave us a model of DNA which indicated a reciprocal relation between two intertwined complementary but oppositely directed strands of this material itself. As this model was based on precise analysis of the x-ray diffraction pattern, it marks a tremendous step beyond mere conjecture toward understanding the actual chemistry of heredity.

This, of course, is only a beginning. The problem of the untwisting of the complementary strands is one that is difficult to contemplate without vertigo, at least if it must proceed through the whole length of the chromonema, with its hundreds of thousands of gyres (*30*). The difficulty would, of course, be mitigated if the DNA were broken up without disruption of order into units with molecular weights of perhaps 10^6 (some 150 gyres) all capable of untwisting simultaneously.

The problem of how DNA imposes patterns on other macromolecules (RNA, proteins, polysaccharides) has not yet advanced beyond the stage of conjecture. Especially disconcerting is the fact that some viruses have only RNA and protein and no DNA at all.

The problems of the chemical basis of heredity are thus far from solved. An important step has, however, been taken, and the nucleic acids, their processes of specific synthesis and of imposition of specific patterns on other macromolecules, have now become the focus of intense effort by biochemists. Genetics and biochemistry have made a contact here that promises to be as fruitful as that of genetics and cytology a generation earlier.

Fine Structure of the Gene

The field that has been investigated most intensively in recent years by distinctively genetic techniques is that of the fine structure of the gene. Present concepts were foreshadowed by the theory of step allelomorphism of Dubinin (*14*) and Serebrovsky (*31*). Oliver's demonstration (*32*) of crossing-over between supposed lozenge alleles in *Drosophila melanogaster*, with reconstitution of wild type, and that by Lewis (*33*) of position effects associated with crossing-over between star and asteroid, probably located in the components of a double salivary band, initiated a period of successful splitting of many supposedly single loci in this organism. Similar results have been obtained in several other organisms, notably maize (*34, 35*), *Neurospora* (*36*), *Aspergillus* (*37*), yeast (*38*), *Salmonella* (*39*), and phages (*40*).

Interpretation has taken two directions. In some cases, subdivision of a system of supposed alleles with multidimensional variability has seemed to yield components with single types of effect, and thus has led to the hypothesis that heredity is made up, after all, of ultimate particles that behave as units both structurally and physiologically. Some proponents of this view have indeed not hesitated to divide seemingly complex loci into simple components on the basis of physiological effect alone. Unfortunately, thorough analysis of the effects in cases in which complex loci have actually been divided by crossing-over has often not indicated any clear-cut separation into physiologically simple loci (*41*). It is probable enough that there are unitary patterns in the genic material, whether divisible by crossing-over or not, that determine patterns in a single macromolecular product, but also that there are a vast number of different sites for mutation and possibilities for multidimensional variability in the activity of this product.

The other interpretation favors complete abolition of the classical structural gene, that is, the view that disruption by crossing-over or by other means, may occur between any two nucleotide pairs of the Watson-Crick molecule. Pontecorvo and Roper (*42*), for example, have pointed out that the ratio of amount

of recombination (5×10^{-4}) between the outer two of three demonstrated components of the white superlocus of *Drosophila* and the smallest amount between two (8×10^{-6}) is 62, and that a similar calculation from four separable mutations in a superlocus of *Aspergillus* gives 150, suggesting the possibility of almost unlimited subdivision. On the other hand, such facts by no means preclude the possibility that there may be particulate loci varying greatly in length and that the intervals between them may vary greatly in ease of breakage, as is indeed suggested by the very heterogeneous appearance of the salivary chromosomes of the Diptera.

The process of actual subdivision of blocks concerned with single physiological processes has gone farthest in studies of phage (*40*) and bacteria (*39*). From estimates of the total number of nucleotide pairs in the phage, it appears likely that there is no limit to divisibility, short of the nucleotide pair.

Interpretation of these cases and of some cases of apparent rare crossing over in higher forms has unfortunately been made somewhat doubtful by the recognition (*43*) of a class of mutations, "conversions," that occur only in heterozygotes, not by crossing-over, although they are likely to occur in the neighborhood of a crossover. This phenomenon, foreshadowed by a study of a mutable locus of *Drosophila virilis* by Demerec in 1928 (*44*), and by Winkler's (*45*) conversion theory of abnormal tetrad ratios in fungi and mosses, is of great interest in itself as a further inroad on the wastebasket category "mutation." Its occurrence also raises the question whether it is pedantic to use even firmly demonstrated crossing-over at rates characteristic of mutation in defining the boundaries of the basic genetic unit. At rates of 10^{-5} or less per generation between similar mutations, crossing-over itself becomes essentially merely another kind of mutation.

Again it is not clear that recombination in the process of synthesis of naked DNA of phage can be considered as the same phenomenon as crossing-over between homologous chromatids of higher organisms, some two orders of magnitude greater in diameter. Thus, even if phage and bacteria are shown to contain no structural genes, it is quite possible that there has been an evolutionary development of such structures with the several-hundredfold increase in the amount of genetic material in higher organisms.

There are some general reasons for suspecting the existence of preferential breakage points in *Drosophila*. Let us assume that the chromonema consists of a succession of physiological units, each involving some thousand nucleotide pairs. If the breakage points of chromosome rearrangements occur at random between nucleotide pairs, there would be only one chance in a thousand that a break would not disrupt a physiological gene and only one in a million that there would be no disruption at either end. Yet 40 percent of 332 random translocations observed by Patterson and his associates (*46*) in *Drosophila melanogaster* were viable as homozygotes, and over 90 percent of these were fertile. Moreover, some or all of the damage may well have been due to disruption of interactions between adjacent genes.

Similarly, crossing-over would usually cause at least isoallelic mutation if one supposes that the population carries many isoalleles at high frequencies in

Table 1. Classification of the biological sciences. The locations of branches of genetics are indicated in italics.

Biological level		Climax phase: Description	Climax phase: Dynamics	History: Description	History: Dynamics	Multiplication
Ecologic system	World biota	Biogeography	Biotic stability	Paleontology	Biotic evolution	
	Local biota	Ecology (community)		Ecologic succession		
Interbreeding population	Species	Taxonomy	Species stability	Phylogeny	Macroevolution; Transformation	Species cleavage
	Deme	Demography; (7) *Population genetics*			Microevolution; (7) *Population genetics*	
Multicellular organism	Individual	External characters	Behavior; (6) *Genetics of behavior*	Life history		Physiology of reproduction; (1) *Formal genetics*
	Organ	Anatomy	Gross physiology	Descriptive embryology	Morphogenesis; (5) *Developmental genetics*	
	Tissue	Histology			Histogenesis	
Cell	Cytoplasm and nucleus	Cytology	General physiology; (4) *Physiological genetics*	(2) *Cytogenetics*		Mitosis
Autonomous macromolecule	Gene	(3) *Theory of the gene*				
	DNA	*Gene chemistry*	*Gene physiology*	*Gene mutation* Description	*Gene mutation* Process	*Gene duplication*
Nonautonomous molecule		Biochemistry				

each physiological unit. Such mutations may well occur, but an evolution toward greater stability of successful patterns would seem likely, if possible.

In addition to such general arguments, we have the intensive study of Muller (*47*) on rearrangements involving a restricted region of the X-chromosome of *Drosophila melanogaster*, which indicated a very limited number of breakage points. The study of the Greens (*48*) of 18 lozenge mutations indicated, in very extensive tests, that these fell into just three groups such that crossing-over occurred between but not within them. The studies of David Bonner (*49*) and his associates in *Neurospora* may also be referred to here.

We must, however, note the possibility that physiologically significant patterns in the DNA are separated by large inert stretches. The results of Patterson and his associates could be accounted for if there is twice as much inert as active material, even if breakage occurs at random.

Mazia (*50*) has found indications that DNA polymers, 4000 A long, are bound together longitudinally by Ca or other divalent ions, which present points of relatively easy separation under certain conditions. Kaufmann and MacDonald (*4*) have, however, questioned this interpretation of the experimental evidence.

Still another possibility, not necessarily exclusive of either of the preceding, is that there is an evolutionary mechanism for protecting useful sequences of nucleotides from disruption. The identification of Belling's ultimate chromomeres with genes has been questioned on the ground that these are observed to be merely sites of incipient coiling in leptotene (*5*), but if, as is generally agreed, they occur always at certain definite sites, they must be indicators of real entities. Precocious coiling of definite regions suggests intrachromatid synapsis of tandem duplications of about the period of normal coiling. Perhaps very short tandem duplications have been very much more common in the course of evolution than even Bridges (*23*) or Metz (*51*) supposed and actually constitute the structural genes by largely restricting breakage to unduplicated intervening regions.

The difficulty may be raised that such duplication would usually interfere with the expression of inactivating mutations. One would, however, expect such duplicants to differentiate, each tending to become inactivated in respects in which the other has retained activity. Moreover, only about 10 percent of the loci of *Drosophila melanogaster* (if identified with salivary bands) seem capable of conspicuous viable mutation, suggesting that most loci actually are protected from this sort of mutation.

It has long been evident that inversions are also very common in the course of evolution. The result of tendencies toward repeated duplication by unequal crossing-over, toward differentiation of the duplicants, and toward the occurrence of inversions of various lengths would be subdivision of the chromonema into regions of more or less similar material, bounded by unconformities. One might consider such regions as supergenes or gene clusters, consisting of several or many highly stable genes (that is, single duplications) separable with varying degrees of difficulty according to the amounts of intervening unduplicated material.

While the modes of origin of physiological genes, that is, physiologically significant patterns of nucleotides, and of structural genes are independent on this view, one would expect natural selection to bring about a tendency toward coincidence and to restrict unduplicated material to regions of no physiological significance, in which disruption, not necessarily at exactly the same level in all strands, would have no physiological consequences.

One of the difficulties of most hypotheses of crossing-over has been the requirement that the exchange points of the two chromatids correspond exactly in position; and this is certainly exacerbated if each consists of numerous separate strands. Belling's hypothesis (*52*) escaped this difficulty by postulating that the genes are connected by extensive nongenic material which produces crossovers in pachytene by shifting of old connections and forming of new ones along lines of minimum distance at half-twists.

A modification of this hypothesis is possible with chromatids, constituted as suggested above, even if the DNA is continuous, by supposing them to be rather plastic where unprotected by internal synapsis of tandem duplications. The duplicated, physiologically active regions correspond to Belling's genes and the unduplicated, physiologically inert regions to his intergenic material.

Under this hypothesis, corresponding regions of the leptotene chromosomes, already with double amounts of DNA (*53*) and with physiologically active regions already forming chromomeres, attract each other to give zygotene. At pachytene, each chromosome divides lengthwise by equational apportionment of ultimate strands into sister-chromatids. The results of Taylor, Woods, and Hughes (*7*) with radioactively marked chromosomes seem to require, as they note, that all newly synthesized strands be apportioned as a block.

We assume that exchanges between ultimate strands are highly improbable if they are parallel, whether within or between chromatids, but that exchange occurs more or less frequently between the crossed strands of the homologous chromatids that are most closely pressed together at an overlap point, established, as in Belling's hypothesis, by accidents of position and pairing in synapsis. We must suppose, moreover, that if such exchange begins, it continues throughout these two chromatids, which thus give rise to shortened crossover chromatids. It appears that the greater the length of an overlap, the greater the chance of exchange at the overlap points (*54*). We must also suppose that there is more or less twisting of sister-strands along each chromosome in order to account for the randomness of the pairs of homologous chromatids that exchange in successive chiasmata, but that this does not bring about sister-strand crossing-over (*55*).

The requirements for accounting for the phenomena of crossing-over are undoubtedly somewhat severe if the chromatids contain many strands. Yet it seems necessary to consider the possibilities in view of the situation revealed by the electron microscope.

Continuing with this model, we may suppose that short double exchanges may occur under very rare conditions among groups of parallel strands, leading to unstable mutations of the conversion type if they occur between strands of homologous chromatids of a heterozygote. Mutations might also arise occasionally from such double exchanges between paired strands of differentiated tandem duplications within a coiled chromomere.

Terminology

Within the boundaries established by rearrangements, we expect a hierarchy of structures with varying degrees of physiological complexity and differentiation, culminating perhaps in differences so great that no relationship can

be recognized. We need a hierarchy of terms. *Locus* should I think be used for systems of multiple alleles, however complex, as long as no cleavage has actually been observed. To divide a locus on the basis of physiological effects alone involves a dangerous begging of the question of structure. If, however, cleavage has been observed, it becomes a question whether one prefers to recognize a single locus with subloci separable at rates like those of mutation, or a superlocus or locus cluster with component loci. In the former case, we should recognize a qualified allelism between separable components. One might use *euallelic* for strict allelism as far as known, and thus *aneuallelic* where there is very rare crossing-over within what seems most convenient to recognize as a locus, on the occasions in which it seems necessary to make a distinction. The terms *identical* and *nonidentical alleles,* which have been suggested (*39*) seem confusing since strict alleles need not be identical physiologically. The terms *homoallelic* and *heteroallelic,* which have also been suggested (*38*) would be appropriate except that they seem too much like the terms *homallelic* and *heterallelic,* which have been used since 1937 (*56*) for important concepts in population genetics. A population is homallelic with respect to a locus if all individuals are homozygous in the same sense; otherwise it is heterallelic. An isogenic population is homallelic in all loci.

It would seem well to restrict *pseudoallelic* to description of genetic relations between loci of a recognized superlocus or locus cluster, because of its implication of spuriousness.

Heterochromatin

Selection may operate to build up a large number of undifferentiated longitudinal replications of a physiological gene. The suggestion of Casperssen (*57*), developed further by Pontecorvo (*58*), that heterochromatin may consist of many replications of a few genes, the products of which are needed in bulk, is an attractive one.

This could account (*59*) for the irregular organization; the easy disruption in some but not all cases (in contrast with the postulated stabilization by one tandem duplication); the tendencies toward apparent non-homologous pairing after rearrangement; easy transposition of probable heterochromatin blocks in maize (*60*); relative dispensability, including that of supernumerary chromosomes (*61*); restriction of observed differential effects on characters to quantitative modifying action (*62*); and the inhibition of the activity of euchromatic genes brought into proximity (*63*).

Large masses of the same active material might be expected to become low points in concentration gradients of raw materials and high points in concentration gradients of products (especially at low temperatures) (*64*). The V-type position effects of masses of heterochromatin on unadjusted genes (*63*), the inhibitory effect on adjacent genes of the transposable elements in maize (*60*), the inhibitory effect of extra Y-chromosomes on sensitive genes of *Drosophila* throughout the genome recently described by Cooper (*65*), and its greater inhibitory effect on other heterochromatin and hence on the V-type position effect itself by double negative action (*66*), may be examples. So also depletion of raw materials may account for negative heteropycnosis under some circumstances in contrast with positive under more favorable circumstances, for slow multiplication where euchromatin is multiplying rapidly (salivary chromosomes of Diptera), and perhaps for unequal effects in different cell lineages (variegation).

One might also, perhaps, expect that the accumulation of many tandem replicates of the same genic material would lead to non-equational mitosis in it and hence to variegation for a different reason. Also to be expected is relatively frequent irregularity in meiosis by unequal crossing-over, especially if there are great differences in number of replicates in parental heterochromatic regions, and thus a sort of semi-Mendelian heredity of any effect. This should simulate somewhat the effect of multifactorial heredity and occasionally contribute something to the mode of heredity of quantitative variability.

These are conjectures. I suspect that experimental work of the next few years, perhaps work to be reported here, will do much to clear up the relations between structural and physiological genes and between euchromatic and heterochromatic ones.

Physiological Genetics

The idea that genes control the properties of cells by determining the enzymes that are present goes back in a sense to the earliest years of the century, and the idea that genes act by imposing specific patterns in the process of synthesis of macromolecules, whether in their own duplication, in the production of antigenic specificity, or in that of the enzymes, is also far from recent (see *67*). These conjectures had, however, little or no real impact on general physiology. Until very recently, the textbooks in that subject rarely made any mention of the gene and treated the cell as the ultimate unit of life.

The real breakthrough came recently when systematic exploration of the control of elementary processes of the mould *Neurospora* was made by the combined efforts of a geneticist and a biochemist, Beadle and Tatum. Now we have a rapid expansion of biochemical genetics or genetic biochemistry (*68*). What had been two almost airtight compartments of biology are now inextricably interwoven.

Studies of the relations of gene and cytoplasm and of cytoplasmic heredity began early with Correns and have continued on a relatively modest side. Nevertheless, some of the most important results of the recent period have been obtained in this field. I regret that the time at my disposal forbids any discussion here. The time seems ripe for a major breakthrough.

Developmental Genetics

A step up in the biological hierarchy is the problem of development. There is not much of a non-speculative character that can be said of histogenesis, which rests on the still enigmatic relations of genes and cytoplasm to which we have referred. With respect to morphogenesis there is at least increasing contact between geneticists and embryologists. There was a period not long ago when experimental embryologists would trace the interactions of various factors in the development of an organ —pressures and tensions, inductions, hormones, neural stimulation, environmental conditions—and perhaps, at the end, list heredity as a sort of magic that operated through other than physiological channels. More recently, many trained embryologists have turned to genetically determined abnormalities as useful material, with illuminating results. The systematic study of the interaction effect of numerous loci on particular characters is especially promising.

The complete analysis of the development of a higher organism nevertheless remains one of the most intractable

problems of science. Perhaps it is beyond human grasp. But I suspect that there will be great advances in understanding and am sure that this can come about only in the conjunction of the two disciplines.

Beyond morphogenesis is the genetics of behavior on which a beginning has been made.

Population Genetics

Finally, we pass to the level of the genetics of populations. To a considerable extent this can bypass the levels of developmental and cellular biology and treat populations merely as systems of gene or aberrational frequencies, subject to various abstract pressures. There has been a considerable mathematical development of theory along this line from fairly early in our history. Somewhat divergent conceptions have been reached, which I have discussed elsewhere (for example, in *69*) and do not propose to go into here. I may say, however, that it is apparent that we need a more adequate theory of quantitative variability, based on generalizations at the levels of physiological and developmental genetics, and also more understanding of the implications of population structures and ecologic relations.

It is hopeful that the recent period has been characterized by rapidly increasing interest in the genetics of human populations, in the study of laboratory population of various organisms, and in studies on a large scale of the genetic properties of populations in nature, such as those under the leadership of Dobzhansky and of Clausen.

In this last we come full circle. The geneticists, systematists, field naturalists, and even the paleontologists find that they have problems that can only be solved by joining forces (*69*).

Conclusion

A subject which at its origin seemed to many to be destined merely to grind out endless 3:1 ratios has penetrated through the biologic sciences from the level of the individual down to a new biological entity at the level of the macromolecule and back through various disciplines to the level of the population. It has become inextricably linked with cytology, biochemistry, general physiology, experimental embryology, the behavioral sciences, ecology, systematics, and even paleontology. If it should ever disappear as a separate discipline, it will only be because all theoretical biology has been bound together into a single field, to a large extent through its efforts. In relating the formerly mysterious, almost magic, subject of heredity to the chemistry of a particular class of molecules, it has also played a major role in binding all science into one coherent whole.

If this unified science indicates from one point of view that all that pertains to the most complex organisms, including man and his behavior, is merely the resultant of laws of nature governing molecules, atoms, and ultimately elementary physical particles and their fields, it indicates from the opposite point of view (*2*) that these same molecules, atoms, and particles are little creatures whose mainsprings of action must be essentially similar in kind to those of their derivatives, the complex creatures in which Dr. Wheeler took such delight (*70*).

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Science in the News

Science Enters the Political Arena

Recently there has been widely publicized evidence that science has at last come into its own in the political arena. Abroad, British Prime Minister Harold Macmillan promised in his election campaign that if he won he would appoint a Minister of Science. In this country, a special task force of the Republican Party's Committee on Program and Progress released a report on "The Impact of Science and Technology," and the Democratic Party's new Advisory Committee on Science and Technology held a press conference at which it urged the establishment of a federal scientific laboratory to "wage peace."

Britain's Science Minister

Now that Macmillan has been reelected, it is reasonably certain that Britain will have a Minister of Science. The Prime Minister described the post in the Conservative Party's election manifesto, "The Next Five Years," a document that is comparable to the platforms presented by the Democratic and Republican parties before a presidential election. The manifesto indicates general lines of policy and makes a few specific commitments. One of these was the appointment of a Minister of Science who would be given the task of promoting scientific and technological development.

After pointing out that it would be wrong to concentrate all government scientific work in a single ministry, the manifesto said that the new minister would have responsibility for the Department of Scientific and Industrial Research, the Medical and Agricultural Research councils and the Nature Conservancy, the atomic-energy program, and the United Kingdom contribution to space research. At a pre-election press conference, Macmillan is reported to have commented that he envisaged giving the science post to one of the Cabinet ministers who had no departmental responsibility, such as the Paymaster General.

The Republicans Study Science

The Republican report on science, which was released on 4 October, was prepared by the Task Force on the Impact of Science and Technology of the Republican Committee on Program and Progress. The task force was headed by Charles E. Ducommun of California, president of the Ducommun Metals and Supply Company. The report, a 15-page pamphlet, strongly endorses President Eisenhower's present administration of science and attempts to establish guidelines and goals for the future.

In general, the pamphlet recommends greater government support of science, especially of basic research, but warns against government control, saying that scientific effort should be widely decentralized and competitive. Coordination should be through discussion and the interchange of papers, not "through administrative fiat."

The report suggests that by 1976 the country should be spending about $36 billion a year "consciously and purposely to expand the scientific revolution." (At present the budget is approximately $10 billion for research and development.) To encourage industrial research, the task force urges tax benefits for private enterprise and patent protection for commercial applications of inventions resulting from work conducted with government funds.

The following three conditions essential to the creation of a strong science and technology are presented and then discussed.

"The maintenance of an environment of freedom and public understanding in which creativity can flourish.

"The maintenance of a superior educational system which stresses the value of excellence for its own sake and which makes a special effort to search out the most gifted minds, wherever found, and to make available to them the most advanced training which they are capable of absorbing.

"The provision of scientists and engineers with the economic resources with which to pursue their search with the utmost aggressiveness."

The release of the Republican pamphlet has special significance, for it marks the first time that any political party has formally conducted a study and issued a report on the impact of science and technology.

In addition to Ducommun, members of the task force are Paul D. Bagwell, Michigan State University; Elmer Hess, former president, American Medical Association; Sigurd S. Larmon, president, Young and Rubicam, Inc., New York; Robert E. Rathburn, professor of architectural engineering, University of Colorado; Claude Robinson, chairman, Opinion Research Corporation; Stephen C. Shadegg, president, S-K Research Laboratories; Paul R. Williams, fellow, American Institute of Architects; and Mildred Younger, lecturer and broadcaster.

Democratic Science Group Speaks

On 11 October, just 1 week after the Republican report was released, the Advisory Committee on Science and Technology of the Democratic Advisory Council, which was formed last spring, held an all-day meeting at Democratic headquarters in Washington to discuss the problems of science and technology in relation to United States foreign and military policy, the U.S. space program, proposals on science and technology for the 1960 Democratic campaign platform, and problems of civilian defense.

However, the chief topic at a midday news conference was the proposal to establish a government laboratory for active study in a scientific manner of methods for maintaining peace. Committee chairman Ernest C. Pollard, head of the department of biophysics at Yale University, conducted the press conference with the assistance of two Nobel-prize-winning committee members, Polykarp Kusch of Columbia University, and Harold C. Urey of the University of California's Institute of Technology and Engineering at La Jolla.

Pollard explained that the proposed laboratory should be an independent agency of the federal government, but that eventually it might become an international body. It would be staffed by

top-level scientists whose first work would be to make "realistic suggestions for meeting the technical problems of disarmament, and meeting them in a professional way on a solid basis." Later, at a reception, Pollard suggested that the agency should be launched with a $50-million budget. Another committee member compared the operation of the proposed organization to that of the Operations Research Organization, pointing out that we should wage peace with the same scientific efficiency that we wage war.

At both the press conference and the reception, committee members noted the lack of scientists on the Republican task force, none of whom are listed in *American Men of Science*. All 17 men in the Democratic group are recognized representatives of the scientific community.

In addition to Pollard, Kusch, and Urey, the members are: Samuel K. Allison, professor of physics, Enrico Fermi Institute for Nuclear Studies, University of Chicago; Harrison S. Brown, professor of geochemistry, California Institute of Technology; Leslie C. Dunn, professor of zoology, Columbia University; Louis B. Flexner, chairman, department of anatomy, University of Pennsylvania; Trevor Gardner, chairman and president, Hycon Manufacturing Company, Pasadena, Calif.; H. Bentley Glass, professor of biology, Johns Hopkins University; David R. Goddard, director, division of biology, University of Pennsylvania; Frank Goddard, Jet Propulsion Laboratory, California Institute of Technology; David L. Hill, consulting physicist, New York, N.Y.; Charles C. Lauritsen, professor of physics, California Institute of Technology; F. T. McClure, chairman, Research Center, Applied Physics Laboratory, Johns Hopkins University; Richard B. Roberts, department of terrestrial magnetism, Carnegie Institution, Washington, D.C.; John S. Toll, chairman, department of physics, University of Maryland; and Gilbert F. White, chairman, department of geography, University of Chicago.

Eight members of the Democratic Advisory Committee on Science and Technology belong to the Federation of American Scientists, an organization that pioneered in the scientist's struggle to be heard in politics. The federation was formed in 1946 by a group of nuclear physicists who felt that Congress should hear the scientists' point of view when it was considering atomic energy legislation. Now that both political parties are giving formal attention to scientific questions, and with legislation pending before Congress, it seems clear that scientific issues will be widely discussed in the 1960 election campaign.

Lunik III Flight to Moon Underscores U.S.-Soviet Positions in Space Competition

Lunik III, the 618-pound Soviet moon rocket, is expected to go around the earth 18 October as it follows the elliptical orbit that first took it around the moon last week. The rocket was launched 4 October, the second anniversary of the launching of the world's first satellite, Sputnik I. Reaction here to the launching and to the developments in the space competition during the last 2 years has been a composite of realistic acceptance of the facts and a growing realization that without the *sine qua non* of space research—rocket boosters in the 1.5-million-pound thrust range—the future can only promise a widening gap between this country's achievements and those of the Soviet Union.

"I wish it were different, but there is nothing you can do to change the clock back." This comment, by Herbert York, the Defense Department's director of research and engineering, reflects both the general view on the latest Soviet moon shot and one of the major reasons for the gap. The Soviet Union is reported to have started its rocket program in 1946, with the aid of a sizable number of German scientists. This country, putting its reliance on bomber-carried atomic weapons, did not start such a program until 1953, when tests in the Pacific showed the feasibility of combining small nuclear warheads with rocket carriers. A crash program was instituted, also with the help of German scientists.

The program, which has been marked by many successes and a number of spectacular failures, has resulted in the orbiting of 12 satellites, including the paddle-wheel satellite that relayed a picture of the earth's cloud cover, and Vanguard III, a 50-pound device launched 18 September. The U.S. satellites have ranged in size from 3 to 450 pounds. Most (and this is regarded as the significant fact) have carried a wide range of finely sensitive—"sophisticated"—instruments that have relayed back miles of taped information on the nature of outer space. The Van Allen radiation belts, for example, were discovered by analysis of this information.

The Russian program has resulted in the orbiting of four satellites, but each, because of its weight and the nature of the experiment involved, represented a major step in the exploration of space. Sputnik II carried the dog Laika. Sputnik III, with a payload of almost 3000 pounds, is the largest satellite ever put in orbit. Lunik III is the first to have circled the moon.

Lunik's Observations Unreported

Although Lunik III was launched almost 2 weeks ago, no concrete information as to its purposes or observations has been reported to the public. At the time of launching it was widely reported that the instrument case contained a camera that would take photographs of the dark portion of the moon. Since 4 October, however, Soviet commentators have not confirmed or denied the earlier report. Nor is factual information available as to whether the satellite passed in front of the moon's path or behind it. Most of the released information on Lunik's progress has been obtained second-hand from the Soviet press agency, Tass. According to these reports, the satellite came within 4375 miles of the moon during its swing around it. A maximum distance from the earth of 291,870 miles was reported. The speed of the satellite varied with the influence of gravity; on the return flight the speed is said to be about 1200 miles an hour. When the satellite reaches the point in its orbit closest to the earth—about 25,000 miles away—it is expected to have a speed of 9000 miles per hour. After it reaches this point Lunik will start on its second outward trip. No prediction has been made about the satellite's life expectancy. Beyond these facts, the United States experts have little information about Lunik. All speculation may be thrown off by the firing of undisclosed "retro" or counter-thrust rockets. Commentators generally agree that the Soviets are making a minimum number of commitments on Lunik to avoid the propaganda risks of missing announced goals.

Among the many comments that followed the Soviet moon shot was one by T. Keith Glennan, administrator of the National Aeronautics and Space

Administration: "We are no further behind them than we were yesterday. But that's far enough." Glennan cited the propulsion problem as the main source of this country's difficulties, suggesting that "in the opinion of our scientists, we lack only the propulsion capacity to match their spectacular feats."

Work on this problem is currently under way among the U.S. agencies concerned with space. Two rockets, the Vega and the Centaur, are now under development and are expected to match the thrust of the rockets currently in use in the Soviet Union. They are expected to be ready in about a year. Two other rockets, the Nova and the Saturn, are being developed for use in the 1960's. These are being designed to have the 1.5-million-pound thrust that is held to be necessary for extraterrestrial contacts. In recent weeks, however, there has been discussion about curtailing the Saturn program for lack of funds.

Economy Delays Program

Although no responsible official has stated that more spending alone is the answer to this country's difficulties in the space competition, there is no question that uncertain financing and periodic budget cuts have delayed the programs that promise to provide boosters of the capacity needed. The possibility of curtailment or cancellation of the Saturn program is only one example. During its last session, Congress made a significant reduction of the funds that the President had requested for the National Aeronautics and Space Administration. The House of Representatives had made a cut of $60 million in NASA's budget. The Senate recommended the full amount of $350 million. In accordance with the usual practice in Congress, the difference was split, and the space agency lost $30 million. At the time of the House cut, the NASA administrator said that action would have "crippling" and "disastrous" consequences with regard to space competition. During the period when Congress was acting on the NASA request, there was a lull in Soviet space activities and the cut was the subject of little debate and little publicity. Recent events, including the launching of Lunik II, which hit the moon, and of Lunik III, can be expected to make the issue of economy in space activities a lively one in the political campaigns ahead.

Call for Space Forum Planned by Soviets

The Soviet Union plans to ask the United Nations to convene an international scientific conference on space research. The call for the conference was made last week by Deputy Foreign Minister Vasily V. Kuznetsov in a speech before the U.N. General Assembly. Reports indicate that the Soviet Union will propose that the meeting be held next year and that it be modeled on the scientific conferences on the peaceful uses of atomic energy that were held in Geneva in 1955 and 1958.

The suggestion for the conference was made during a long speech on disarmament that included a discussion of the problems of outer space. Kuznetsov cited recent advances, including the Russian moon shot, and mentioned the need for cooperation in space activities. Following this, he said: "Taking into account the benefits of the exchange of experience in the field of scientific research accomplishments for a more rapid progress in exploring outer space, the Soviet Government intends, in particular, to put forward the proposal to convene under United Nations auspices an international conference of scientists on the exchange of experience in exploring outer space."

Response Favorable

The response to the proposal was generally favorable among the delegates. The United States and Britain approved the suggestion, thus virtually assuring that such a conference would be held. "We welcome this new departure in Soviet policy and hope that it means cooperation in the future work of the United Nations in the field of outer space," Ambassador Lodge said in a statement issued later. In London, the British Foreign Office said that it had no details on the proposal, but that ". . . we very much welcome the Soviet intentions. Our policy is to encourage the fullest possible international exchange on these matters." Similar responses were made by the leaders of other delegations at the U.N.

Some doubt has been expressed that such a meeting could be held before the last quarter of next year because of the lengthy preparations that would be required. If the model of the "atoms-for-peace" conferences were followed, elaborate displays of devices and techniques would be in order, as well as the submission of technical papers dealing with all aspects of outer space exploration. Policies on security and declassification would also have to be devised.

Another Meeting Planned

In addition to the projected conference, another space forum is scheduled for next year. This is the meeting of the Committee on Space Research of the International Council of Scientific Unions. The committee is an outgrowth of the International Geophysical Year and seeks to find ways to continue the cooperation in space research that characterized the IGY. The meeting is set for next January and will be held in France. The committee, as a unit of ICSU, is non-governmental in nature, and concerns itself with purely scientific matters, such as advanced notice of space probes, tracking, exchange of data, and the provision of room on space vehicles for experiments prepared by scientists in countries that have no space capabilities. One of the early efforts of the committee was to get international cooperation on the matter of avoiding contamination of the moon.

Although the Soviet Union has voiced objections on the imbalance of the committee representation between Communist and neutralist nations and Western-bloc nations, it is reported that these difficulties are being worked out. The result may be two major exchanges of space data in the coming year, with the Soviet participating in both.

Canadian Atomic Energy Moves Ahead

Canada and Euratom, the six-member European atomic energy pool, have entered into two agreements for a $10-million peaceful atomic energy exchange program. The first agreement, valid for 10 years, lays down the legal conditions for exchange of source material and special nuclear material on commercial terms, and for exchange of information, technical advice, and training facilities. Under the second agreement, Atomic Energy of Canada Limited will make available its experience with a natural-uranium fueled heavy-water-moderated type of reactor.

The $10 million is to be contributed over 5 years, half by Atomic Energy of Canada, to be spent in Canada, and the other half by Euratom, to be spent in its member countries — France, West

Germany, Italy, the Netherlands, Luxembourg, and Belgium.

Manitoba Research Center Planned

In another announcement, Atomic Energy of Canada reports that it will build a new nuclear energy research and development center in Manitoba. At present Canada's only major nuclear research center is the Chalk River establishment on the Ottawa River, about 150 miles west-northwest of Ottawa. However, the government-owned company has a Nuclear Power Plant Division in Toronto and a Commercial Products Division in Ottawa.

The management of Atomic Energy of Canada Limited feels that the Chalk River center cannot operate at maximum efficiency if it continues to expand. Among the major facilities at Chalk River are four research reactors, including the NRX and NRU reactors, particle accelerators, and chemical and metallurgical plants. The number of workers is approaching 2500, of whom some 400 are university graduates.

Chalk River Reactor School

A further development in Canadian atomic energy is the announcement that the first class in the newly established Chalk River Reactor School will begin 1 February 1960. Canadian and foreign engineers and scientists may apply for admission to the school, which will have a class of 20 students in each 12-week course.

The school was set up in response to the wide interest shown in the atomic power systems being developed in Canada. The course of studies places special emphasis on power reactors moderated with heavy water and fueled with natural uranium, such as the 20,000 kilowatt NPD (Nuclear Power Demonstration) station now under construction near Rolphton, Ontario, and the 200,000 kilowatt CANDU (Canadian Deuterium Uranium) station to be built north of Kincardine, Ontario.

The Chalk River Reactor School will not duplicate instruction being given by universities. Candidates for the school must have a university degree in physics, engineering physics, chemistry, metallurgy, or engineering. The school will give these graduates first-hand knowledge not only of power reactors but also of the advanced research and engineering test reactors.

Director of the Reactor School is D. A. Keys, scientific adviser to the president of Atomic Energy of Canada Limited, and secretary is W. R. Livingston, head of the Office of Industrial Assistance. Lecturers are senior company executives and members of the staffs of the various AECL divisions in Toronto, Ottawa, and Chalk River.

Application forms may be obtained from Canadian embassies or consulates or from the Secretary, Chalk River Reactor School, Atomic Energy of Canada Limited, Chalk River, Ontario. Completed application forms for the first course must be received at the secretary's office not later than *15 November*.

U.S. and U.S.S.R. Exchange Scientific Fishery Knowledge

Five American fishery scientists have returned home after an extensive inspection in August of Russian salmon fisheries, and five Russian fish experts have arrived in the United States to observe American salmon activities, the Department of the Interior reports. The trips were arranged for an exchange of scientific and practical fishery information.

The Russians are touring the Pacific Northwest and Alaska and will return to Washington about 21 October. Their itinerary includes inspection of salmon hatchery operations and the work of fish nutrition and fish disease laboratories. They will see the operations of privately owned can companies, canneries, and fish freezing and cold storage facilities.

The American mission to the Russian salmon areas had a double purpose—to give U.S. specialists an opportunity to learn of Russian fishery operations first hand, and to secure fish and fish blood samples of known Russian origin for a long-range internationtal salmon study which has been in progress for about 3 years. Members of the American group report success in both aims, stressing that their hosts were especially cooperative.

The North Pacific salmon study is a three-nation project—Japan, Canada, and the United States are participating. One purpose of this study is to secure data upon which nations of Asia and North America may base salmon management plans. A specific problem is to determine the place and the extent of intermingling of the American and Asian races of salmon during the time the salmon are at sea. This in turn necessitates the development of a system of differentiating American from Asian fish. Research has indicated that probably the most reliable way to differentiate between the two races is by blood type.

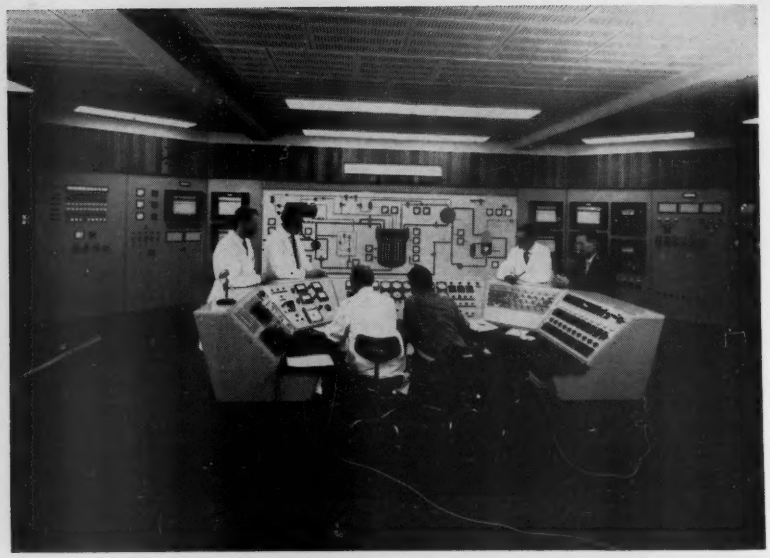
At the Bureau of Commercial Fisheries Biological Laboratory at Seattle, Washington, considerable work has been done on this project on salmon and blood samples from Japan, Canada, and the United States salmon areas. No salmon unquestionably of Russian origin were available for study until this exchange visit, when the Russians, although their salmon fishing season in most areas was closed, let the American visitors take fish out of streams on the Kamchatka peninsula.

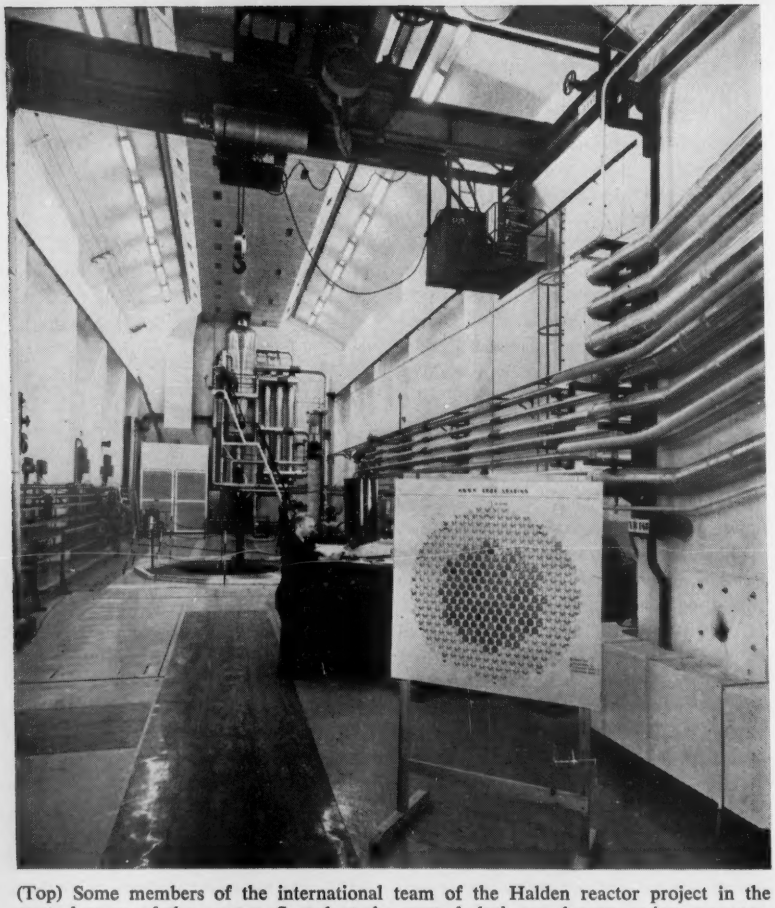
Research Grants To Be Used by Defense Department

The use of grants for the support of basic research is now permitted in the Department of Defense. The department, acting after a long delay, last month issued a directive implementing a law passed last September which gave the department and a number of other federal agencies authority to use grants as well as contracts. Prior to passage of the law the research contract had been the only means of support for basic research that could be used by the department. Grants, unlike contracts, demand neither detailed plans nor detailed accounting.

The effect of the law, P.L. 85-934, was to liberalize the terms by which some federal agencies, previously limited to contracts, could provide grants for research. Several agencies—the National Science Foundation and the Department of Health, Education and Welfare, for example—already had such authorization and hence were not affected by the act. The principal agencies affected were the Department of Defense, the Atomic Energy Commission, the National Bureau of Standards, and the newly created National Aeronautics and Space Administration.

The Bureau of Standards and NASA have been making use of grants for some time as have some divisions of AEC. The new Department of Defense directive, which became effective 25 August, represents the initiation of the practice by the governmental agency which spends the greatest amount of money on scientific research.





(Top) Some members of the international team of the Halden reactor project in the control room of the reactor. Seated at the control deck are deputy project managers Kjell Petter Lien (Norway) and N. Rydell (Sweden). Standing are (from left to right) Magnus Oevreeide (Norway), Heinz Braun (Germany), Henk Buis (Netherlands), and J. Deshong (U.S.A.). (Bottom) Halden reactor hall as it appears from the entrance tunnel. The display board in the foreground shows the present core loading. The reactor pit is in the middle of the floor, with the steam drum in the background.

King Olva Opens Heavy Water Reactor at Halden

King Olav of Norway opened the world's first boiling heavy water reactor at Halden, south of Oslo, on 10 October. The reactor was built by the Norwegian Institutt for Atom-energi and is to be used for an international cooperative research program that is being sponsored by the Organisation for European Economic Cooperation. In addition to Norwegian scientists, the Halden research group includes investigators from Austria, Denmark, Euratom (representing Belgium, France, Germany, Italy, Luxembourg, and the Netherlands), Sweden, Switzerland, and the United Kingdom. The joint project was organized by the OEEC European Nuclear Energy Agency.

The reactor has been working at low power levels since 29 June. The power level will be gradually increased toward the ultimate design level of 20,000 kilowatts (heat).

New Curriculum Introduced at Stanford

The Stanford University School of Medicine's new curriculum, which went into effect on 30 September in the new $22-million Medical Center, inaugurates a program in which basic science is taught according to subjects or areas of unified interest, rather than along departmental lines. Laboratory work is carried out in small multidiscipline laboratories employing almost exclusively the experimental approach. Individual courses in anatomy, physiology, and biochemistry, among others, have given way to cooperative courses planned and executed by committees made up of representatives of the departments concerned. An integrated course presents the fundamental principles concerning the biological aspects of man in terms of normal structure and function.

At Stanford the total medical school program is 5 years, most of the students entering at the end of 3 years of college work. The basic medical sciences are spread out over the first 3 years. In addition an amount of time equivalent to 1 academic year is devoted to nonmedical work, work that is carried out during the first 3 years. The Stanford program is similar to one that Western Reserve University has had in effect for about 6 years.

Another Arkansas Dismissal

In late August this section reported the names of four professors at the University of Arkansas who were dismissed for refusing to comply with a new Arkansas statute, generally regarded as a measure to oppose the National Association for the Advancement of Colored People, that requires all publicly employed teachers to list the organizations to which they have belonged or to which they have contributed during the past 5 years.

Inadvertently, the name of Robert S. Ely was omitted. Ely, an associate professor of pediatrics, was also among those forced to resign. He is now in private practice in Salt Lake City. An observer comments:

"I feel he was a true loss to academic pediatrics and that he should receive recognition for making this very difficult decision. Several of his faculty colleagues reversed their decision at the last moment in order to avoid the inconvenience such a decision entailed. Dr. Ely refused to betray his principles and was a leader in organizing the test of legality of this unfair act, prior to his dismissal."

Grants, Fellowships, and Awards

General graduate. The National Academy of Sciences–National Research Council has again been called upon to advise the National Science Foundation in the selection of candidates for the foundation's program of graduate and postdoctoral fellowships. The foundation plans to award approximately 1100 graduate and 125 postdoctoral fellowships in these two programs during the 1960–61 academic year. Committees appointed by the Academy–Research Council will evaluate applications of all candidates; final selection will be made by the foundation.

Open only to citizens of the United States and awarded solely on the basis of ability, the fellowships may be used for advanced study in the mathematical, physical, medical, biological, and engineering sciences, including anthropology, psychology (excluding clinical psychology), and the following social sciences: geography, mathematical economics, econometrics, demography, information and communication theory, experimental and quantitative sociology, and the history and philosophy of science. The awards are open to college seniors, graduate and postdoctoral students, and other individuals with equivalent training and experience.

All applicants for graduate (predoctoral) awards will be required to take an examination designed to test scientific aptitude and achievement. This examination, administered by the Educational Testing Service, will be given on 16 January 1960, at designated centers throughout the United States and certain foreign countries.

The annual stipends for graduate fellows are as follows: $1800 for the first year; $2000 for the intermediate year; and $2200 for the terminal year. The annual stipend for postdoctoral fellows is $4500. Limited allowances will also be provided for tuition, laboratory fees, and travel.

Further information and application materials may be obtained from the Fellowship Office, National Academy of Sciences–National Research Council, 2101 Constitution Ave., NW, Washington 25, D.C. The deadline for the receipt of applications for regular postdoctoral fellowships is *22 December 1959*, and for graduate fellowships, *1 January 1960*.

Teacher training. The National Science Foundation will support about 200 In-Service Institutes for Secondary School Teachers of Science and Mathematics during 1960–61. Proposals are now being accepted from universities and colleges interested in participating in this program, which is designed primarily to assist colleges and universities to encourge teachers in local and outlying school districts to take advantage of scientific training facilities not otherwise readily accessible to them. During the academic year just beginning, about 8600 secondary school teachers will be enrolled in these after-school institutes.

Directions for preparing proposals may be obtained from the Institutes Section, National Science Foundation, Washington 25, D. C. Deadline for submission of completed proposals is *30 November*.

News Briefs

National Science Youth Month is being observed throughout October. Under the auspices of Science Service, Washington, D.C., high school students and their science teachers, joined by 33 national civic, professional, industrial, labor, and educational groups, are taking part in the observance. In a special statement, President Eisenhower has urged participation in National Science Youth Month in communities everywhere as a means of strengthening all phases of education and of stimulating in young students a regard for the traditions of intellectual excellence.

* * *

The Senate Committee on Interstate and Foreign Commerce will hold a series of public hearings in Alaska during the latter part of October on pending bills, including S. 1889, which authorizes the establishment of the Arctic Wildlife Range. Persons desiring to testify are asked to notify the committee, Room 5108, New Senate Office Building, Washington, D.C., where the hearings schedule is available. A witness must submit in advance ten copies of the statement he expects to present.

* * *

More than 750 delegates from all parts of the United States are expected to attend a conference on science and technology in Israel and the Middle East to be held in New York during the weekend of 31 October and 1 November. Sponsored by the American Technion Society, 1000 Fifth Avenue, New York, N.Y., as a means of bringing together the best of scientific thinking to spur the industrial development of Israel —and to demonstrate to Israel's neighbors the benefits of modern technology —the conference will be held at the Hotel Statler in New York.

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Last month the Engineers Joint Council, New York, released the first issue of *Engineer*, a bulletin to report pertinent national affairs and EJC activities.

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National Medical Fellowships, Inc., has announced that the Alfred P. Sloan Foundation has granted $60,000 for ten 4-year medical-school scholarships to promising Negro college students. Of the 220,831 physicians throughout the country, only about 4000 are Negro; thus, in comparison with a ratio of one doctor to 815 people for the entire nation, there is only one Negro physician per 4500 Negroes. Since it was founded in 1946, National Medical Fellowships, Inc., has awarded $819,333 in fellowships, scholarships, and loans to 262 Negro men and women pursuing medical careers.

Scientists in the News

The winners of the American Heart Association's 1959 Howard W. Blakeslee Awards are as follows:

Ben Pearse, free-lance writer, for two articles in the *Saturday Evening Post*: "The Pill with the Built-in Surprise," published 4 October 1958, and describing the use of the new drug chlorothiazide in the treatment of heart failure, kidney disease, and high blood pressure; and "Spare Parts for Defective Hearts," published 30 August 1958, and relating to the development of plastic materials for use in treating improperly operating heart valves.

"Open-heart surgery," a CBS-TV film presented a part of the Conquest series on 9 March 1958. It showed the teamwork of Walton Lillehei and his associates in open-heart surgery on a 6-year-old girl at the University of Minnesota Medical School. The program was sponsored by Monsanto Chemical Company.

"Operation tracer," a television program in the Heart of a Child series, presented by WBBM-TV, Chicago, which began 9 June 1958. It described a disease-protection program through which a child was safeguarded from rheumatic fever and possible rheumatic heart disease.

Each of the winners received an honorarium of $500.

Owen T. Gribbin, product development manager with Standard Brands, Inc., Sherburne, N.Y., has been named chief food chemist with Foster D. Snell, Inc., New York.

Scientific visitors to the United States from the United Kingdom include the following:

J. S. Garside, senior principal scientific officer on the staff of the Houghton Poultry Research Station (Agricultural Research Council), arrived 15 October and will leave 25 November. His itinerary includes: Canada, California, Michigan, New York, Massachusetts, Connecticut, and New Jersey.

E. Orr, senior scientific officer of the Economics Division at the Tropical Products Institute, Department of Scientific and Industrial Research, London, arrived 11 October and will leave 30 October. Her itinerary includes Washington, D.C., and San Francisco.

H. E. Newall, principal scientific officer, Warren Spring Laboratory, Department of Scientific and Industrial Research, London, arrived 6 October and will leave 28 October. His itinerary includes: Washington, D.C., Pennsylvania, Ohio, Illinois, Utah, California, Tennessee, and New York.

Frank Manov, senior technical staff member at Space Technology Laboratories, has been appointed supervisor of a newly formed satellite and space defense studies group at Electro-Optical Systems, Inc., Pasadena, Calif.

B. H. Colvin, mathematician of the Physical Research Unit at Boeing Airplane Company, has been appointed head of the Mathematics Research Laboratory, Boeing Scientific Research Laboratories, Seattle, Wash.

Rev. **Placidus Reischman** has been appointed head of the department of biology at St. Martin's College, Olympia, Wash.

The National Science Foundation has appointed the following new program directors in its Division of Biological and Medical Science:

Roy P. Forster, on leave of absence as professor of zoology at Dartmouth College, has been appointed program director for regulatory biology. He will administer research grants for the study of regulative processes in organs and organ systems.

Dwight D. Miller, on leave of absence as professor of zoology at the University of Nebraska, has been appointed program director for genetic biology. He will administer research grants for study of the nature, action, and transmission of genes and chromosomes in individuals, families, and populations of living organisms.

Meredith N. Runner, research scientist with the Roscoe B. Jackson Memorial Laboratory, has been appointed program director for developmental biology. He will administer grants for the study of plant and animal embryology, fertilization, morphogenesis, differentiation, growth, regeneration, and physiology of reproduction.

Francis J. Reithel, on leave of absence as professor and head of the department of chemistry at the University of Oregon, has become program director for molecular biology. He will administer grants studying the structure and reactivity of biologically important macromolecules such as proteins, nucleotides, and hormones, as well as various aspects of physical biology.

Edwin J. Wellhausen, director of the Rockefeller Foundation's agricultural program in Mexico, has been appointed associate director for the agricultural sciences. In his new position he will direct the foundation's recently created inter-American corn improvement program, which will chiefly involve research in Latin America.

The recipients of the 1960 awards of the American Chemical Society include the following:

Herbert C. Brown, professor of chemistry at Purdue University—ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by the Synthetic Organic Chemical Manufacturers Association.

Charles D. Coryell, professor of chemistry at Massachusetts Institute of Technology—ACS Award for Nuclear Applications in Chemistry, sponsored by the Nuclear–Chicago Corporation.

E. L. Jack, professor of dairy industry at the University of California, Davis—ACS Award in the Chemistry of Milk, sponsored by the Borden Company Foundation, Inc.

Elias J. Corey, professor of chemistry at Harvard University—ACS Award in Pure Chemistry, sponsored by Alpha Chi Sigma Fraternity.

Arthur F. Scott, professor of chemistry at Reed College—Scientific Apparatus Makers Award in Chemical Education.

Neal R. Amundson, professor and head of the department of chemical engineering at the University of Minnesota—ACS Award in Industrial and Engineering Chemistry, sponsored by the Esso Research and Engineering Company.

Arthur B. Pardee, associate professor of biochemistry and virology, University of California, Berkeley—Paul-Lewis Laboratories Award in Enzyme Chemistry.

James D. Watson, associate professor of biochemistry at Harvard University —Eli Lilly and Company Award in Biological Chemistry.

Robert W. Taft, Jr., professor of chemistry at the Pennsylvania State University—ACS Award in Petroleum Chemistry, sponsored by Precision Scientific Company.

P. J. Elving, professor of chemistry at the University of Michigan—Fisher Award in Analytical Chemistry.

The presentation of the awards will take place at the spring meeting of the association in Cleveland, Ohio.

Book Reviews

The Incas of Pedro Cieza de León. Translated by Harriet de Onis. Victor Wolfgang von Hagen, Ed. University of Oklahoma Press, Norman, 1959. lxxx + 394 pp. Illus. $5.95.

In 1535 a 13-year-old Spanish boy, from Llerena in Estremadura, sailed from Seville to Cartagena. There he joined one of the armies of exploration and conquest that were being formed and set off into the interior. Fifteen years later he emerged at Lima, Peru, as a mature soldier preparing to return to his homeland. His journeys and trials had not brought him great wealth, but the things he saw and reflected upon during all this time were chronicled in a manuscript that he took back to Spain with him. This man was Pedro Cieza de León, one of the great soldier-historians of the Spanish conquest of the New World, a man who ranks along with Bernal Diaz del Castillo in his ability to relate an event with straightforwardness more vivid than the purplest prose.

Between 1535 and 1550 Cieza had served with such men as Robledo, Belalcázar, and La Gasca. He had seen the Cauca Valley and the Quimbaya Indians. He entered Quito when the memories of Atahuallpa were still alive. And he had been on the plain at Xaquixahuana when La Gasca broke the forces of Gonzalo Pizarro to end Peru's bloody civil wars in 1548. Commissioned as an official historian by La Gasca, Cieza spent the next two years traveling through Peru and Bolivia making a systematic inquiry into Inca history and culture. This, in brief, was the experience detailed in eight books of which only the first had been published when Cieza died in 1554.

Cieza was a man with strong humanist leanings, and his writings revealed his concern over the European mistreatment of the Indians. Because of the critical nature of his comments on this subject, his plans for the publication of the remainder of his work ran afoul of the Inquisition. His manuscript was, in effect, impounded in the archives of the Council of the Indies where, except for some pirating and plagiarizing late in the 16th century, it was forgotten. A bad translation of a part of his first book was published in English in 1709, but it remained for W. H. Prescott to "rediscover" Cieza when he drew upon this remarkable source for his *Conquest of Peru*. Later, Sir Clements Markham published the whole of the first two books in English; and there have been subsequent Spanish editions and other English translations of both the first two books and of sections of other books.

The present Onis-Von Hagen edition utilizes those parts of books 1 and 2 which deal with Cieza's travels in the domain of the Inca between 1547 and 1550. The original chapters have been rearranged, however, so that they follow the traveler on his journey from north to south. Other chapters have also been assembled to form a kind of Inca ethnography and history. In each case the chapters are labeled to show their original provenience and position in the Cieza volumes. The whole has been put together with a long introduction by Von Hagen, and interlaced through the book are a series of 32 excellent half-tones illustrating the landscape and archeological monuments which Cieza saw and described. This is a very effective presentation, and it serves to give the work a great popular appeal without in the least detracting from its scholarly qualities.

The De Onis translation is the finest in English, and I think there is little doubt that this rendering of Cieza de León is the best all-round presentation of both the man and his writings which has yet appeared in print. Von Hagen shows great perceptiveness, imagination, and feeling in his creation of the historical contexts, both immediate and on the larger scale of 16th-century world politics.

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The Relation of Fungi to Human Affairs. William D. Gray. Holt, New York, 1959. xiii + 510 pp. Illus. $8.50.

This is a textbook designed for a somewhat unusual type of course which might be called "economic mycology"—a specialized branch of "economic botany." This may seem, to the outsider, to be rather too much concentration on too limited a subject, but in this one will soon agree with the author that, in fact, the subject is far greater than can possibly be contained in 510 pages. Gray, however, does an excellent job of making a clear and well-organized summary of the field. He begins with a brief description of the morphology and classification of the fungi, and then divides the major portion of the book into two sections: the "Beneficial activities of fungi," and "Harmful activities of fungi." Let me just list the topics covered, for the magnitude of the activities of fungi are indeed impressive. Under the beneficial activities we find the destruction of organic wastes; mycorhizae; fungi as food and their role in food processing (especially cheese); fungi in medicine (especially antibiotics, but many other topics as well); alcohol fermentation; the syntheses of gallic, citric, gluconic, itaconic, and kojic acids, as well as various enzymes, glycerol, and fats; the use of fungi in bioassays; and then a fair group of miscellaneous activities. Among the harmful aspects we find plant diseases, timber and paper destruction, tropical deterioration of materials and objects, food spoilage, and medical mycology (allergies, mycoses, and mushroom poisoning).

The material presented in the summary of each of these subjects is well chosen to give an effective picture. Furthermore, it is a modern picture for the author has taken pains to bring the topics discussed up-to-date. If the reader wishes to pursue any of these large topics further, there is a well selected bibliography at the end of each chapter.

It should be reemphasized that this is a textbook and not a literary essay, such as, for instance, John Ramsbottom's *Mushrooms and Toadstools*. In fact, the two books, both excellent in their own way, are at opposite poles (and there are others that lie somewhere in between). Ramsbottom's style is lively and witty, while Gray's is wholly unobtrusive. Ramsbottom concentrates on a few topics of special interest, while Gray gives a balanced and well-rounded

picture of the whole field. It would be fitting, in a course of "economic mycology," that Gray's book should be used as a text and Ramsbottom's as collateral reading.

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The Cell. Biochemistry, physiology, morphology. vol. 1. Jean Brachet and Alfred E. Mirsky, Eds. Academic Press, New York, 1959. xxi + 816 pp. Illus. $22.

This is the first of a series of three books which will cover most of cell biology in some 40 articles written by well-known workers in the field. This volume is in two parts, the first on methods, the second on general problems. The remaining two volumes will deal with cell constituents and specialized cells. Every biological library should, and no doubt will, buy the series, but its price puts it beyond the means of the individual biologist. The production is excellent and up to the high standards of the publishers. The indexing is good and so are the illustrations (except for the absence of figure captions in Ebert's article).

The best part of this volume is the section on general problems. There is an excellent article by Grobstein on the difficult field of cell differentiation. It is an intractable field at the moment, but it is still the central problem in cell biology. Briggs and King give a good review of the interactions of nucleus and cytoplasm in eggs and embryos and include a summary of their own important work. It is a pity that it could not have been extended to cover recent research with micro-organisms. Ebert gives a clear and critical account of the immunological approach to biological specificity. This is a rapidly developing subject and one of great interest to all biologists, but at the moment the approach is at the level of tissues and whole organisms and has not yet come down to the level of the cell. There are also articles on fertilization, sex determination, radiation effects, and plant cell growth and differentiation (which shows the wide gap between plant and animal cell biologists).

The section on methods is too short to be really useful. The articles cover a wide field and cannot be much more than summaries of the available methods—Wyckoff on optical methods, Gersh on fixation and staining, Glick on microchemical techniques, and White on tissue culture. The best reviews are those which cover a narrower field—Allfrey on cell fractionation, and Walker and Richards on microscopical methods for measuring single cells. In view of the fact that the same publishers are producing a series of books on general cytochemical methods, I doubt whether this section is really necessary.

I must admit that I experience a slight sinking feeling when handling this book: 800 pages are a weight both for mind and hands. Surely it would have been better to split this into half-a-dozen or so smaller books: For the authors, this would mean greater personal responsibility and, more freedom for individual views. For the editors, less pressure to collect contributions by a given date. For the readers, ease of handling, less mental indigestion, and the possibility of buying some of the books. For the librarian, the fact that six books can be read by six different people at the same time. At its price, it is hard to believe that this book would cost much more if it were so divided.

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Soviet Reviews of Nuclear Science. On the 40th anniversary of the October Revolution. Pergamon Press, New York, 1959. 110 pp. Illus. $5.

This slim volume was first published in the U.S.S.R. in November 1957 as a special number of the journal *Atomnaya Energiya* in celebration of the 40th anniversary of the Soviet Revolution. This excellent English translation now appears under the auspices of Pergamon Press.

The volume consists of eight papers, the longest of which is devoted to a review of high-energy particle research in the U.S.S.R. Next in length are reviews of work on low-energy neutron interactions and of the use of radioisotopes in the U.S.S.R. Short, additional papers describe Soviet work in radiochemistry and the development of atomic energy in the Soviet Union.

The quality of the contributed papers is generally proportionate to the length; the Soviet scientists apparently find it difficult to say much in areas where security consciousness still runs high.

The paper on high-energy physics by Dzhelepov and Pontecorvo reviews the use of the synchrocyclotron at the Joint Institute of Nuclear Studies. First completed in December 1949, this accelerator was modified in 1950 and again in 1953 so that it finally achieves proton energies of 680 Mev. The experimental work conducted with this accelerator since 1949 is described in detail. The paper contains a large number of graphs, taken from the Soviet literature, which summarize the experimental findings on high-energy interactions. Much of the apparatus used in these experiments—such as cloud chambers, bubble chambers, and a magnetic spectrometer—is shown in photographs. A clear, running account of the state of the field of high-energy physics at the time of the experiments is given. Non-Soviet work, both theoretical and experimental, is duly noted where necessary.

The review of low-energy neutron interactions was written by Vladimirsky, Panov, Radkevich, and Sokolovsky. After a discussion of the measurements and the instruments used for this work, the state of the field is summarized, including the current knowledge of the distribution of neutron widths and level spacings, the dependence of the strength function, mean level spacing, and radiation width on atomic weight, and the less systematic data on fission parameters. The improvement in the theoretical fit of the strength function, when the asphericity of the nucleus is taken into account, is shown. However, the review is, in some respects, already out-of-date. Thus, the Porter-Thomas model of the statistical distribution of neutron widths has already gained general acceptance, and so has Wigner's model of the distribution of level spacings.

The papers on radioisotopes and radiochemistry will be of interest to workers in these fields, and indicate that the extent of work in these fields is comparable to that in the United States.

The four papers on nuclear reactors are much more sketchy and incomplete. The paper by Nikolaev outlines the development of atomic energy expected in the Soviet Union during the sixth Five Year Plan. The reactors proposed for construction are only briefly described, although further details have since been released. Generally, it is stated that the program in the U.S.S.R. has aims similar to those of the United

States' atomic energy program—to obtain experience with different, full-scale, atomic power plants in order to determine their economic potential. An incentive for atomic power, lacking in the United States, is the higher cost of fuel transportation, since the major use of electric power is in the European part of the U.S.S.R. while the major coal fields are in the East. It is clear that Russian engineers do not agree on the economic aspects of nuclear power any better than their Western counterparts. Nikolaev expects the large pressurized-water reactor to yield electricity at lower costs than coal fired stations, a statement contradicted by other spokesmen for the U.S.S.R.

The remaining papers include a sketch of the superheated-steam, uranium-graphite reactor. Cost figures for the fuel are taken from non-Soviet sources. Similarly, the paper on graphite in nuclear reactors leans heavily on non-Soviet sources of information. Finally, a paper by Novikov on the efficiency of atomic power stations makes the point that regenerative heating plays only a minor role in nuclear power plants compared with the role it plays in conventional steam plants.

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Bumblebees. John B. Free and Colin G. Butler. Macmillan, New York, 1959. xiv + 208 pp. Illus. $5.00.

This readable book, one of the latest (No. 40) in the 'New Naturalist' series, was first published in England. The authors are on the staff of the bee department at the Rothamsted Experimental Station.

In the opening chapters, Free and Butler discuss the bumblebees' life history, including such topics as the founding, growth, and decline of the colony, reproduction, the division of labor, and the enemies of the bumblebees. Subsequent chapters go more deeply into behavior and treat the collection and storage of nectar and pollen, flower relationships, and locality learning. The economic importance of bumblebees in the pollination of certain forage and fruit crops is covered in a separate chapter. The final chapter, "Bumblebees and their relatives," is somewhat mistitled, for almost all of it is devoted to a comparison of the habits of bumblebees with those of only one relative, the honey bee.

The book contains four appendixes. The first and second are treatises on the collection and study of bumblebee colonies and on how to start colonies in captivity. These will be very useful to anyone who wishes to study the behavior of these insects. The other two appendixes, by I. H. H. Yarrow of the British Museum (Natural History) will be of no interest to most American readers, because they contain keys to the British bumblebees and distributional notes on the British species.

Free and Butler are to be congratulated for this admirable compilation of the life history and behavior of bumblebees; the compilation is based on their own observations, as well as on the voluminous scientific literature devoted to these fascinating insects. Bumblebees are of more than ordinary interest because they belong to one of the few groups of insects which have evolved a social life. The enjoyable text is enhanced by Butler's excellent black-and-white photographs showing some of the details of life history and flower visits. The book is a worthy companion to Butler's earlier book in the same series, *The World of the Honeybee.*

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New Books

Germany Rejoins the Powers. Mass opinion, interest groups, and elites in contemporary German foreign policy. Karl W. Deutsch and Lewis J. Edinger. Stanford Univ. Press, Stanford, Calif., 1959. 336 pp. $6.50.

A Handbook for Dissectors. J. C. Boileau Grant. Williams & Wilkins, Baltimore, Md., ed. 5, 1959. 455 pp. $5.

Industrial Gums. Polysaccharides and their derivatives. Roy L. Whistler, Ed. Academic Press, New York, 1959. 777 pp. $25. Each chapter describes a specific gum. This description includes source, constancy of supply and composition, cost and cost variation, chemical structure and reactions, history, uses, derivatives and their uses, and physical properties, including those of its solutions, gels, and films.

Introduction to the Theory of Quantized Fields. N. N. Bogoliubov and D. V. Shirkov. Authorized English edition, revised and enlarged by the authors. Translated from the Russian by G. M. Volkoff. Interscience, New York, 1959. 736 pp. $17.

Introductory Nuclear Theory. L. R. B. Elton. Interscience, New York, 1959. 297 pp. $6.40.

Life and the Universe. Archibald C. Huntsman. Univ. of Toronto Press, Toronto, Canada, 1959. 122 pp. $3.

Metamorphosis. On the development of affect, perception, attention, and memory. Basic Books, New York, 1959. 352 pp. $6.

Nuclear Electronics. Proceedings of the international symposium on nuclear electronics organized by the French Society of Radioelectricians. International Atomic Energy Agency, Vienna, Austria, 1959 (order from International Publications, 801 Third Ave., New York). 464 pp. $4.

Numerical Methods for Nuclear Reactor Calculations. Gurii Ivanovich Marchuk. Translated from Russian. Consultants Bureau, New York, 1959. 295 pp. $60.

Reflexes to Intelligence. A reader in clinical psychology. Samuel J. Beck and Herman B. Molish. Free Press, Glencoe, Ill., 1959. 683 pp. $8.50.

Reprints

Albert Einstein: Philosopher-Scientist. vols. 1 and 2. Paul Arthur Schlipp. Harper, New York, 1959 (reprint of ed. 1, Tudor, 1949 and 1951). 781 pp. $1.95 each.

Ancient Science and Modern Civilization. George Sarton. Harper, New York, 1959 (reprint of ed. 1, Univ. of Nebraska Press, 1954). 111 pp. $0.95 This book reproduces in full the text of the three Montgomery lectures given by Sarton at the University of Nebraska in 1954. Titles of the lectures are "Euclid and his time," "Ptolemy and his time," and "The end of Greek science and culture."

Beyond Psychology. Otto Rank. Dover, New York, 1959 (reprint of ed. 1, 1941). 291 pp. $1.75.

New Pathways in Science. Sir Arthur Eddington. Univ. of Michigan Press, Ann Arbor, 1959 (reprint of ed. 1, Cambridge Univ. Press, 1934). 333 pp. $1.95. The Messenger lectures which Eddington delivered at Cornell University in 1934 are contained in this volume. Chapters 2 and 8 have been added; the other chapters correspond to the 12 lectures.

Out of the Sky. An introduction to meteoritics. H. H. Nininger. Dover, New York, 1959 (reprint of ed. 1, 1952). 356 pp. $1.85. Nininger, director of the American Meteorite Museum, describes famous meteorite landings and craters, and tells how to locate, identify, and preserve a meteorite that survives its fall through the atmosphere.

Science Since 1500. H. T. Pledge. Harper, New York, 1959 (reprint of ed. 1, Her Britannic Majesty's Stationery Office, London, 1939). 357 pp. $1.85. This short history of mathematics, physics, chemistry, and biology was described by A. R. Hall as "still the outstanding one-volume handbook for the history of science during the last four centuries. . . . For this period Mr. Pledge's book provides an encyclopedic wealth of information and ideas such as can be found nowhere else." Thomas S. Kuhn calls it "the most useful one-volume reference work in English for the general technical history of post-Newtonian science."

Reports

Measurement of Human Heart Rate during Usual Activity

Abstract. A small, rugged, self-contained cumulative heart-beat counter has a transistorized amplifier, a watch movement made into a counter, and a battery. The counter is activated by each *R*-wave of the electrocardiographic complex obtained from newly designed precordial electrodes. Heart beats can be counted for as long as 24 hours.

The human pulse rate is usually expressed as the number of heart beats per minute. The normal rate varies from less than 50 to more than 120 per minute, depending on many factors, one of which may be the act of taking the pulse. Pulse rates for longer than a few minutes have been obtained with the electrocardiograph, but the equipment is bulky and the activity of the tested individual is limited. Quantitative data on heart rate in beats per many minutes to many hours during various kinds of activity and work are not available.

In cooperation with engineers of the Illinois Bell Telephone Co. (L. Harrington, W. B. McCreary, L. J. Murphy, and L. Ryan) we have developed a small, rugged, self-contained "pulse counter" capable of totaling heart beats over periods ranging from a few minutes to more than 24 hours (*1*). The counter is packaged as a single unit containing an amplifier, cumulative counter, and power source. It measures 9.0 by 7.0 by 1.5 cm and weighs 100 gm. The instrument is connected by a flexible cable to precordial electrodes (Fig. 1).

The *R*-wave of the electrocardiographic complex is selectively amplified by 5 *R-C* coupled transistor stages. Each pulse of output current (10 ma) activates an electromagnet (100 ohms) which attracts a spring-loaded armature. Each excursion of the armature displaces a modified pallet fork which releases one tooth of the escapement gear of a spring-wound watch movement. In this way the *R*-wave is recorded on the watch face as ⅕ of a second. The modified watch movement with a conventional 12-hour dial, operating as a cumulative counter, can record up to 216,000 heart beats occurring at rates from less than 40 to more than 150 per minute. A pen-light battery supplies sufficient current to operate the pulse counter for more than 24 hours.

The electrodes must conform to rather strict specifications if a signal free of distortion is to be obtained during strenuous activity or for long periods of time, or both. Conductive contact between skin and a lead wire is made by a cylinder of electrode jelly contained in a soft rubber well 0.5 cm deep. The lead wire supported by the rubber well is held 0.25 cm from the skin surface, preventing direct contact between skin and the lead wire (see upper electrode, Fig. 1). A circular sheet of fine-mesh cotton gauze is cemented to the base of the well, providing a large area for fixing the electrode to skin. The gauze base is dipped in dilute rubber cement and allowed to dry completely. The skin site for the electrodes is cleaned, treated with aluminum chlorohydroxide to limit perspiration, and covered with a thin film of liquid latex surgical adhesive which is allowed to dry. The rubberized gauze base of the electrode is pressed onto the prepared site, producing an immediate firm bond. The well is then filled with electrode jelly and capped with a disk of pliable plastic (see lower electrode, Fig. 1).

The flexible gauze base allows free skin movement, and the electrodes remain firmly attached for as long as 72 hours. The electrodes can be detached easily with ether. The lead wires of the electrodes are connected to the counter by a thin flexible cable 35 cm long. The counter is carried in a shirt or blouse pocket. During the first few hours after application of the electrodes, contact resistance decreases, altering the effective input voltage to the low-impedance amplifier (3000 to 5000 ohms). A gain control in the amplifier compensates for this change.

In order to measure the accuracy of the pulse counter, a second means for counting heart beats simultaneously with the pulse counter was needed. By using the precordial electrodes described above with a direct-writing recorder, electrocardiograms with stable base

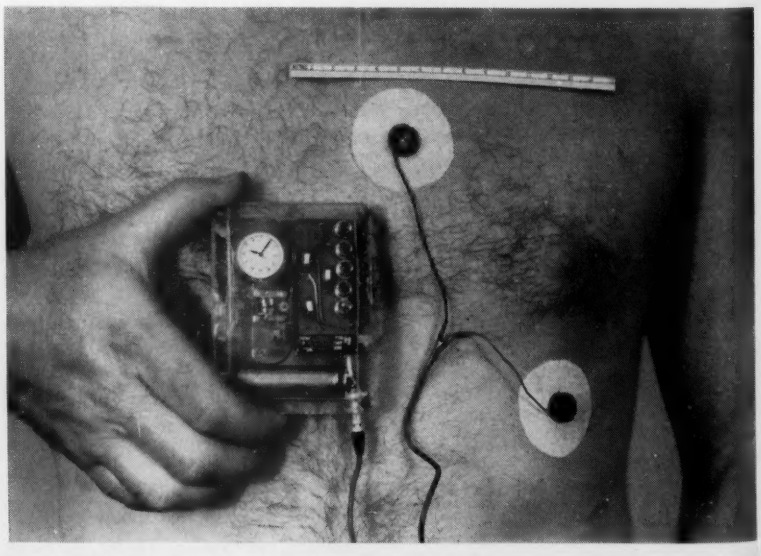

Fig. 1. Pulse counter and precordial electrodes. The upper electrode well is empty and shows the lead wire. The lower electrode well is filled with electrode jelly and capped.

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper.

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* **125**, 16 (1957)].

lines could be obtained. For checking the accuracy of the pulse counter, an additional set of precordial electrodes was applied and connected by long lead wires to a direct-writing electrocardiograph. The *R*-wave counts on the electrocardiogram have been compared with 3000 heart beats recorded by the pulse counter. Check periods include 15 minutes of vigorous exercise, 15 minutes lying in various positions, and the remaining time sitting and walking. During three consecutive 24-hour counts on one of us (D.A.R.), check electrocardiograms were obtained eight times at 8- to 12-hour intervals. The differences between pulse counter counts and electrocardiogram *R*-wave counts ranged from 0.1 to 3.8 percent with a mean of 1.3 percent. (The error in reading the pulse counter dial is up to ± 5 heart beats at the beginning and at the end of a test period. A difference up to 0.3 percent between the two methods for counting 3000 heart beats could, therefore, be expected.) Similar results have been obtained during 24-hour counts on one other man and on two women, all between the ages 32 and 36. During many additional check periods, the pulse counter has functioned with a similar degree of accuracy in men and women in other age groups.

When the pulse counter was used for 24-hour counts, a log of standard time, pulse counter time, and activity was kept, with entries made at about hourly intervals during waking hours. The three consecutive 24-hour counts noted above were 117,000, 115,000 and 122,000. Average minute rates calculated from the logs were 65, 68, and 66 while asleep and 88, 91 and 92 while awake. Average minute rates calculated from hourly counts while awake ranged from 70 to 110. By keeping a log, much additional information about pulse rates during different activities can be obtained.

In our studies we are concerned with the effect of factors such as age, sex, and occupation on pulse rates of apparently healthy people in whom differences in minute rates obtained by the usual means are probably small. A pulse count per 24 hours of usual activity, integrating the amplitude, duration, and frequency of variations in rate over a reasonable physiological cycle, may reveal larger differences among individuals. The pulse counter may also be used for other measurements of heart rate—for example, during work, physical training, disease, or therapy.

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Note

1. This investigation was aided in part by a grant from the Chicago Heart Association; the work by Seymour Glagov was done during the tenure of a research fellowship of the American Heart Association.

13 August 1959

Vitamin-A Content of the Frog Eye during Light and Dark Adaptation

Abstract. Rhodopsin is synthesized from 11-*cis* retinene (vitamin A aldehyde), but releases all-*trans* retinene when bleached by light. In the frog, both isomers of vitamin A are stored in the eye. Total ocular vitamin A, including that bound as retinene in rhodopsin, remains constant during light and dark adaptation. Stores of 11-*cis* vitamin A, however, diminish in the light and are replenished in darkness.

The bleaching and synthesis of rhodopsin involve a cycle of stereoisomerization of retinene (vitamin A aldehyde). Rhodopsin is synthesized from 11-*cis* (neo-*b*) retinene, but releases all-*trans* retinene when bleached by light. Each of these isomers is reduced reversibly by alcohol dehydrogenase and diphosphopyridine nucleotide to the corresponding isomer of vitamin A (*1*).

Vitamin A is stored in the retina and pigment layers (pigment epithelium and choroid) of the eye, and may thence exchange via the blood with stores in other tissues (*2*). However, ocular vitamin A is not in equilibrium with other stores. For example, in cattle up to 65 percent of the vitamin A in the eye may have the 11-*cis* configuration (*3*), whereas this isomer has not been found in other tissues (*4*).

Several years ago, Wald showed that in frogs the bulk of the vitamin A released upon bleaching rhodopsin, leaves the retina during light adaptation, and re-enters during dark adaptation to re-form rhodopsin (*2*). However, he did not decide whether the vitamin A leaves the eye altogether, or is merely transferred from the retina to the pigment layers.

Table 1 shows that *Rana pipiens* has more vitamin A in its eye (retina and pigment layers) when light adapted than when dark adapted. However, if one includes the retinene bound in rhodopsin, the total remains essentially constant in light and darkness. It seems, therefore, that during light adaptation there is a flow of vitamin A from retina to pigment layers, which is reversed during dark adaptation (*4a*). This process is no doubt facilitated by the close anatomical contact between these tissues (see *5*).

The proportion of 11-*cis* vitamin A fluctuates in light and darkness as shown in Table 2. In the light, about 10 percent of the vitamin A has the 11-*cis* configuration, but the concentration increases to about 25 percent during 6 hours of dark adaptation.

Taken together, Tables 1 and 2 show that the frogs of group A, which contained about 1.7 μg of vitamin A per eye, stored about 0.17 μg (that is, 10 percent) as the 11-*cis* isomer when light adapted. After 6 hours of dark adaptation, however, the eye contained about 0.94 μg of the 11-*cis* isomer: 0.24 μg (24 percent of 1 μg) as 11-*cis* vitamin A, and 0.7 μg bound in rhodopsin. During this period in darkness, therefore, 0.7 to 0.8 μg per eye, or about half the vitamin A, was isomerized to the 11-*cis* configuration. Similar computations for the frogs of group B show that during the dark period about 0.9 μg of vitamin A per eye—about one-third of the total—was isomerized to 11-*cis*.

The percentage of stored 11-*cis* vitamin A begins to rise after about 3½ hours of dark adaptation, which is roughly the time it takes for rhodopsin

Table 1. Vitamin A content of the frog eye (*R. pipiens*) following light or dark adaptation in vivo. Temperature 22° to 23°C. In each experiment, three frogs were either light adapted 1 hour in a white pan, illuminated with two 75-watt lamps with reflectors, or dark adapted 6 hours. Following light adaptation, the eyes contained no detectable rhodopsin; after dark adaptation, their rhodopsin content was maximal. The retina and pigment layers were dissected and extracted together. Dark-adapted eyes were dissected in dim red light, light-adapted eyes in diffuse room light. To determine free vitamin A, tissues were ground with anhydrous sodium sulfate and extracted with petroleum ether. Rhodopsin was determined as follows: the tissues were ground with anhydrous sodium sulfate under red light, and vitamin A was extracted as above. The powder was then bleached in white light to convert rhodopsin to retinene and opsin, and retinene was extracted with acetone containing 0.5 percent water. All extracts were transferred to chloroform, and vitamin A and retinene were determined by the antimony chloride reaction. Experiments were performed with two groups of frogs (A and B), which differed as shown.

Exp.	Vitamin A (μg per eye)		
	Free	Bound in rhodopsin	Total
	Group A: dark adapted		
1	1.2	Not measured	
2	1.1	Not measured	
3	1.0	0.7	1.7
	Group A: light adapted		
3	1.8	Negligible	1.8
4	1.7	Negligible	1.7
	Group B: dark adapted		
2	1.9	Not measured	
3	2.6	0.7	3.3
4	1.9	0.7	2.6
	Group B: light adapted		
1	2.8	Negligible	2.8
3	3.25	Negligible	3.25
4	2.6	Negligible	2.6

synthesis to be completed in frogs at this temperature (*6*). Most of the 11-*cis* vitamin A therefore accumulates only *after* the opsin in the rods has been converted to rhodopsin.

The 11-*cis* isomer of retinene or vitamin A is formed from the all-*trans* isomer, probably exclusively in the eye (*4*). The present experiments show that in the frog this isomerization occurs in the dark. The same mechanism presumably operates in the light. However, in darkness the 11-*cis* isomer is initially used for rhodopsin synthesis up to the limit set by the opsin content of the eye (about 0.7 μg equivalent of vitamin A in these animals), and then an excess is stored as 11-*cis* vitamin A. In the light, on the other hand, rhodopsin bleaches, yielding all-*trans* retinene, whereas 11-*cis* retinene is continuously used for its resynthesis. This, in effect, constitutes a mechanism for converting 11-*cis* to all-*trans* retinene. The ocular content of 11-*cis* vitamin A is therefore depleted in the light, and replenished in darkness.

A specific enzyme concerned with isomerizing retinene—retinene isomerase—has been identified in the eyes of cattle and frogs (*7*). It does not act directly on vitamin A. In the dark, it catalyzes the isomerization of all-*trans* or 11-*cis* retinene to an equilibrium mixture containing both isomers in the approximate proportion 95 : 5. Light displaces the equilibrium in favor of the 11-*cis* isomer, but this probably does not occur in vivo for reasons which have been discussed elsewhere (*7, 8*).

The proportion of 11-*cis* vitamin A stored in the dark-adapted eye far exceeds what one would expect from the "dark" equilibrium catalyzed by retinene isomerase. If this is the enzyme involved, special mechanisms must be present for trapping or otherwise stabilizing the 11-*cis* isomer. Such trapping could involve the binding of 11-*cis* vitamin A by specific proteins, or its selective esterification (see *3, 9*). There is as yet no evidence that either process operates in the eye. Indeed, it is entirely possible that additional pathways exist for isomerizing all-*trans* vitamin A or retinene to the 11-*cis* configuration (*10*).

Table 2. Percentage of 11-*cis* vitamin A in eyes of frogs (groups A and B), dark or light adapted as described in Table 1. Free vitamin A was extracted as has been described, and the percentage of 11-*cis* vitamin A was determined by isomerization with iodine in the dark (*11*), or upon illumination (*3*). The percentage of 11-*cis* vitamin A in the light-adapted animals represents a steady state value, which is not changed appreciably by prolonging the light adaptation.

Exp.	Percentage of 11-*cis* vitamin A	
	Dark adapted	Light adapted
A-1	19	11.5
A-2	27	7
B-3	27.5	12
B-4	23	8
Av.	24	10

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4 June 1959

North-South Asymmetry of the Earth's Figure

O'Keefe, Eckels, and Squires (*1*) have reported that a periodic variation of the eccentricity of the orbit of Vanguard satellite 1958β_2, which coincided in period with the revolution of the line of apsides, indicates a third zonal harmonic in the geoid—that is, a north-south asymmetry in the earth's figure; the Northern Hemisphere has a longer axial semidiameter but a smaller mid-latitudinal semidiameter than the Southern Hemisphere—that is, the earth is slightly pear-shaped. Earlier, King-Hele and Merson (*2*) had suggested that a north-south asymmetry might explain perturbations observed in the orbit of sputnik 2. O'Keefe *et al.* conclude that the asymmetry "indicates a very substantial load on the surface of the earth" and further that it is contrary to the view of Heiskanen and Vening Meinesz (*3*), and of geodesists generally, that the earth's gravitational field is very nearly that of a fluid in equilibrium.

Neither of these conclusions necessarily follows from the new figure, which can be reconciled with the Heiskanen and Vening Meinesz concept if it is assumed that the mean density of the mantle in the Southern Hemisphere is a little less than that in the Northern. Such a density variation is consistent with recent tectonic hypotheses based on an expanding earth (*4, 5*).

In an analysis of the first-order deformations of the earth's surface, I have concluded that, contrary to the commonly accepted hypothesis of contraction, the earth is an expanding body, that it has been expanding since before the Cambrian period, that the rate of expansion has been increasing with time, that since the beginning of the Mesozoic era the Southern Hemisphere has expanded substantially more than the Northern Hemisphere, and finally that the rotational consequences of the differential expansion have resulted in a first-order shear system between the Northern and Southern Hemispheres which has determined the pattern of post-Palaeozoic orogenesis.

According to the expanding earth hypothesis, less dense mantle and a geoid surface above the theoretical spheroid might be expected in areas of post-Palaeozoic orogenesis and below "new" oceans (Arctic, Atlantic and Indian oceans, the Mediterranean Sea, and the Pacific Ocean west of the Andesite line), and a geoid depressed below the spheroid and regionally denser mantle might be expected under the older continental blocks and the older oceanic segments (about half of the present Pacific Ocean). Taken collectively, these large areas of one-sign anomaly would produce a geoid which would be pear-shaped when generalized to the third zonal harmonic. They would also produce the semblance of triaxiality which has been found empirically by many

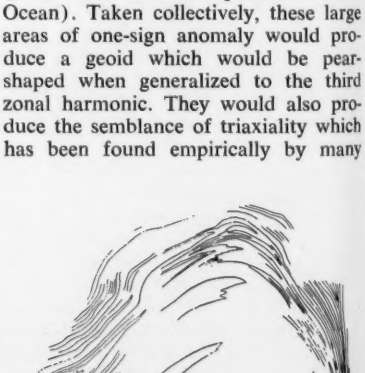

Fig. 1. Fold pattern of the Malaspina Glacier in plan (width of lobe, 25 km).

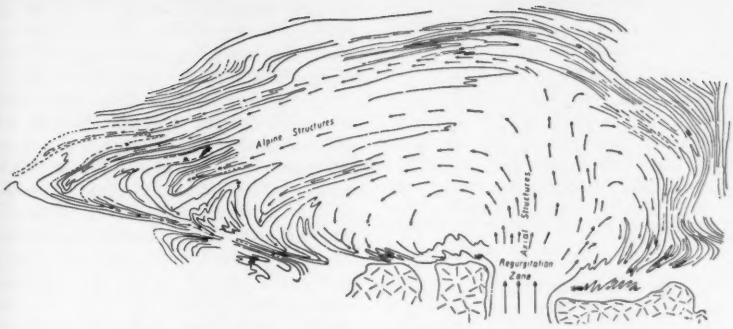

Fig. 2. Fold pattern of asymmetric orogen in cross section.

geodesists. These departures of the geoid from a rotational spheroid would still be in approximate fluid equilibrium and would not imply crustal loads of the order claimed by O'Keefe and his coauthors. They would cause a polar wandering with rheid adjustment until the rotation axis coincided with the maximum inertia axis. This also clears up the conflict reported by Munk (*6*) who found that, in the absence of such asymmetries, the pole should have migrated to Hawaii and, on accepted values for viscosity, should have arrived there within 10^5 years, whereas the palaeomagnetic data indicate that the pole has been moving slowly in the opposite direction and has not been far from its present position since the early Tertiary.

Crustal contraction has been axiomatic for so long that an expanding earth is still liable to rejection as irresponsible heresy. Originally the hypothesis of earth contraction stemmed from the idea of a cooling earth. Although this basis has long since been removed, and more recently reversed (*7*), geologists have still clung to contraction because of the false notion that the folding so universally observed in rocks necessarily indicates crustal shortening, even though I showed (*8*, p. 93) that complex folds of the type found in the hearts of orogens do not necessarily imply shortening. More recently (*4*, *5*) I have pointed out that at all but those shallow zones where the overburden load is less than the unconfined compressive strength, crustal extension yields a triaxial stress ellipsoid with all stresses positive, an environment which may produce boudins and tectonite fabrics and conjugate shears typical of orogenic zones, and further that even megastructures such as the orogens themselves do not necessarily imply crustal shortening. Figure 1 shows the fold pattern of the Malaspina Glacier, traced directly from Sharp (*9*), and Fig. 2 shows a typical cross-section of an asymmetric orogen such as the Alps, with a steep root zone and recumbent folds and nappes, with immense horizontal transport. However, Fig. 2 is drawn from Fig. 1 simply by up-ending it and reducing the ratio of the vertical and horizontal scales to simulate the flattening effect of gravity. Both the Malaspina Glacier in plan and the Alpine orogen in section exhibit similar features of fold and overthrust patterns, and in both the deformed material has developed complex tectonite fabrics, but whereas the lobe of the Malaspina Glacier has visibly increased in width tenfold during the generation of the folds, the Alpine orogen is imagined to have been reduced in width by a comparable order!

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27 May 1959

The hypothesis of fluid equilibrium does not seem to be consistent with Carey's suggestion that the density in the mantle in the Southern Hemisphere is less than that in the Northern.

Since the density varies with depth, the two hemispheres can be compared only at corresponding depths—that is, on corresponding geopotential surfaces. But the condition of fluid equilibrium demands that the density on a given geopotential surface be constant. If it is not, then the pressure, which is the weight of the overlying mass, will be greater in those regions where the density is greater. This will cause the heavier fluid to move out laterally and underrun the lighter fluid everywhere, until perfect stratification is brought about.

Heiskanen and Vening Meinesz point this out, remarking on the subject of fluid equilibrium:

"The condition to be fulfilled is that all equipotential surfaces be at the same time surfaces of equal density" (*1*).

Jeffreys makes the same point (*2*). The result is very well established. It is impossible to have hydrostatic equilibrium at the same time that the density is less at a given depth in the Northern Hemisphere than in the Southern Hemisphere.

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25 August 1959

Instatement of Stuttering in Normally Fluent Individuals through Operant Procedures

Abstract. Normally fluent subjects were required to read from printed pages, and a recording was made of nonfluencies until a stable rate was established. A persistent shock was then introduced. Its cessation for a limited period was made contingent upon nonfluency. Chronic stuttering was instated and eliminated as a function of the change in stimulus.

In operant conditioning, the response is brought under stimulus control through the arrangement of consequences explicitly contingent upon the response (*1*). In a previous study, stuttering responses by chronic stutterers from a speech clinic were brought under stimulus control to a considerable extent by this procedure (*2*). When each stuttering response was followed by noxious stimuli, stuttering was attenuated, and when, with the same subjects, each stuttering response temporarily eliminated these stimuli, the stuttering rate rose.

Stuttering has often been considered an emotional blocking; it can, however, be regarded as a unit of verbal behavior (*3*); that is, breaks, pauses, repetitions, and other nonfluencies can be considered operant responses, having in common with other operants the characteristic of being controllable by

Table 1. Response slope for results reported by subject and experimenter, expressed in degrees.

Reporter	Base line period			Escape period			Extinction period			
	1	2	3	1	2	3	1	2	3	4
Session 1										
Subject	4	12	9	28	32	30	18	16	12	
Experimenter	4	10	8	26	31	27	20	13	14	
Session 2										
Subject	12	14	16	55	52	52	55	49	30	19
Experimenter	12	10	13	51	50	50	52	41	27	15

ensuing consequences. For the chronic stutterer, such nonfluencies may have been immediately followed by consequences which did not occur in connection with regular speech, thereby becoming isolated as response units. Some consequences, such as attention on the part of the listener, noninterruption, and the like, may increase the likelihood of occurrence—that is, may be reinforcing. If stuttering can develop in the manner indicated, then it should be possible to turn nonfluencies of normal subjects into chronic stuttering.

In the experiment previously reported, speech therapists defined moments of stuttering. In the experiment discussed here, the subject was trained prior to the experiment to press a microswitch with each nonfluency. Training continued until the experimenter considered the subject's responses valid. The instructions for this training, plus the instruction to read, the warning that there might be occasional shocks, and the advice that the subject could stop the experiment, constituted the experimenter's only communication with the subject. All recordings and scheduling involved automatic electrical equipment. Tape recordings were kept of the readings. Stuttering was operationally defined as any hesitation, stoppage, repetition, or prolongation in the rhythmic flow of vocal behavior.

The subject sat in a small room and read from printed pages. When the cumulative recorder depicted a smooth base line—that is, indicated regularity of response rate—conditions were changed. An electric shock (24 v, direct current) was pulsed at the rate of ten shocks per second into a 5:1 transformer with 2000-ohm resistance, connected to the secondary circuit; the room lights simultaneously flickered at the same rate. Each pressing of the microswitch by the subject turned off the shock and eliminated the flicker for 10 seconds. The subject could thus completely eliminate both, by responding at 10-second or shorter intervals.

Responses by one subject are recorded in Fig. 1. In the first session, during ordinary reading, nonfluent responses occurred at a fairly regular rate, as depicted in the low slope of the base-line period. At point A_1, the shock-flicker period began, each marker indicating onset of shock and flicker. The curve shows an increase in nonfluencies, leading to less frequent shock, as shown by less frequent markers. At point B_1, extinction began. The shock-flicker was disconnected, and the response rate dropped toward its base-line value.

In the second session, 2 days later, the slope of the base-line period was similar to that of the preceding session. At point A_2, the shock-flicker condition was reintroduced. Upon presentation of the first shock, the response rate rose so markedly that only one further shock, indicated by S_2, occurred during the entire period, when the response rate started to fall. At point B_2, the shock apparatus was disconnected. Since nonoccurrence of shock while the apparatus is connected results in a high rate of response, this rate of response is maintained when the apparatus is disconnected. Eventually, some slackening of response rate occurs, and since the consequences of a high rate of nonfluencies no longer differ from the consequences of a low rate, the response rate returns to base level.

A validity check of the subject's reports of stuttering was made independently from a tape recording, by a speech therapist who pressed a microswitch connected to the cumulative recorder at each response he defined as stuttering. Each test period was divided into three equal periods (except for the extinction period on the second day, which was divided into four parts), and slopes for the responses reported by the experimenter and by the subject were plotted and compared. The results are presented in Table 1, which indicates similar ordinal relationships.

The subject's speech outside the booth was normal. In a third trial, a week later, stuttering was controlled by the flickering light, without shock, and the sessions were discontinued for obvious reasons.

When questioned after the sessions, the subject of Fig. 1 reported that he had stuttered a great deal but ascribed this to his anxiety over his inability to read simple passages. He reported disliking the shock but said it was irrelevant to his behavior in the booth.

A second subject responded in the same way but did not return. A third subject did not initially show the same effect, but a change in procedure brought his stuttering responses under stimulus control: When the light was steady, there was no shock, but when the light flickered, a shock was occasionally presented. Response shut off the flicker for 10 seconds, after which it reappeared. The response rate rose rapidly, and periods of flickering dropped from 131 during the first 20 minutes to 3 for the next 12 minutes, when the session was terminated. A fourth subject exhibited nonfluencies so

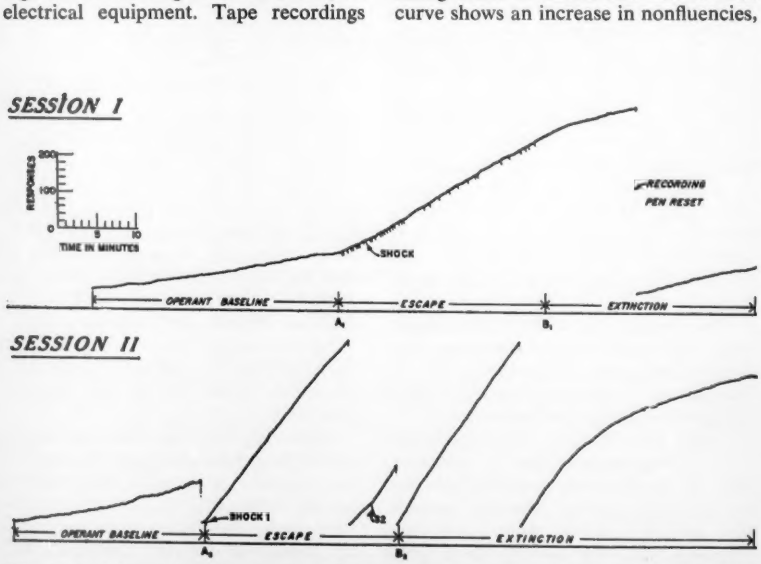

Fig. 1. Instatement and elimination of stuttering responses in a normally fluent individual through control of response-contingent consequences.

rarely that conditioning could not be established during the session.

None of the subjects in these tests reported a history of any previous speech difficulties, and their nonfluencies outside the laboratory are of the type that occur in normal speech.

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7 August 1959

Effects on Palate Development of Mechanical Interference with the Fetal Environment

Abstract. Operations employing various combinations of amniotic fluid withdrawal and release of the embryo from enveloping membranes were performed just prior to the time of normal palate closure. Observations on subsequent palate development led to the hypothesis that fetal membranes can compress the fetus and cause cleft palate when pressure in the amniotic sac is reduced.

Puncturing the amniotic sac with a hypodermic needle just prior to closure of the secondary palate can cause cleft palate in fetal mice (*1*). To explain this effect, it has been suggested that amniotic fluid leaks out and hydrostatic pressure in the amniotic cavity is reduced, the uterus thus being allowed to compress the fetus. The fetus' head would then be pressed against its chest, the lower jaw and tongue being forced up toward the nasal septum. Since the palatine shelves have to force the tongue away from the nasal septum before they can come together and fuse (*2*), pressure on the tongue from below could prevent normal palate closure (*1*).

To test this hypothesis of uterine compression, several modifications of the amniotic sac puncture experiment have been tried (*3*). Thirty-four pregnant mice of heterogeneous origin were treated 13⅔ days postconception, and 25 were treated 14⅓ days postconception. The treatment consisted of exposing the uterus by an abdominal incision under ether anesthesia and subjecting all the embryos of one uterine horn to one of the following manipulations: (i) withdrawal of amniotic fluid; (ii) withdrawal of amniotic fluid and release of the embryo (with its amnion-yolk sac) by slitting the uterus lengthwise; (iii) release of the embryo from the uterus without removing any amniotic fluid; (iv) release of the embryo from both the uterus and amnion-yolk sac membranes. The other horn was left untouched or else was subjected to a manipulation other than the one used on the first horn. Amniotic fluid was removed with a No. 25 or No. 27 needle (these gave the same results, qualitatively) on a microsyringe, and the quantity withdrawn was approximately 1/50 ml (although the total loss varied because of leakage through the puncture hole). The females were reopened at 18⅓ days, the condition of the fetuses was recorded, and the living fetuses within their membranes were transferred to Bouin's fixative.

Table 1. Pooled results for fetuses treated at 13⅔ and 14⅓ days postconception and collected at 18⅓ days.

Treatment	No. of fetuses with		No. of fetuses resorbed
	Normal palate	Cleft palate	
Amniotic fluid withdrawn	24	23	104
Fluid withdrawn + release from uterus	34	18	89
Release from uterus	37	0	51
Release from all membranes	3	0	37
Control (to release from uterus)	13	2	29

The results are shown in Table 1. Release from the uterus obviously does not protect the fetus from developing a cleft palate. However, the cleft palates that develop in released fetuses are still dependent on loss of amniotic fluid, since the control fetuses released from the uterus did not develop clefts. Perhaps the amnion-yolk sac membranes can exert sufficient pressure to account for the cleft palates that developed in the released, amniotic fluid-deficient fetuses. Release of fetuses from both the uterus and fetal membranes would have provided a good test of this possibility, but the resorption rate was so high following this radical procedure that not enough fetuses could be collected to provide a reliable answer (Table 1).

To investigate further the cause of clefts in the released, fluid-deficient fetuses, 20 females were treated at 13⅔ days, and 64 living fetuses were collected at 14⅔ or 15⅓ days, postconception. It had been observed for fetuses collected at 18⅓ days that those subjected to a decrease in amniotic fluid were severely compressed if they had been left within the uterus, but were not noticeably compressed if they had been released from the uterus at the time of treatment. However, when collected at 14⅔ or 15⅓ days, both groups showed mild signs of compression, such as grooving of the body by the umbilical cord or limbs twisted out of position. Since the degree of fetal compression at the critical time for palate development is comparable in both groups, compression may be due to the amnion-yolk sac membranes in both cases. The radical compression caused by the uterus arises at a later time and is not necessarily involved in the development of the cleft palate. In Table 1, two cleft palates are listed for fetuses that were untreated except that the adjoining uterine horn had been incised. Under these circumstances there is some tendency for the fetuses to shift out of position toward the open horn (that is, the lateral pressure had decreased). Perhaps this is another expression of the sensitivity of palate development to changes in pressure relationships (*3*).

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26 June 1959

Long-Term Effects of Tenotomy on Spinal Monosynaptic Response in the Cat

Abstract. Section of the Achilles tendon in the cat resulted in a shortening of the latent period and an increase in the amplitude of the spinal monosynaptic response from gastrocnemius nerves investigated 28 to 42 days after tenotomy. No change was observed in the course of posttetanic potentiation.

Following tenotomy, the muscle is prevented from exerting effective tension and is also deprived of passive stretch. It is thus quite feasible to assume that as long as regrowth of the tendon does not take place, the muscle proprioceptor end-organs (both muscle spindles and tendon organs) are considerably restricted in function, since the natural stimuli for their activation —that is, active and passive tension— are practically eliminated by tenotomy.

Tenotomy could then serve as an experimental approach for studying questions of the use and disuse of central synapses activated by proprioceptors. In the present experiments the spinal monosynaptic response was investigated from nerves innervating muscles immobilized by tenotomy.

Unilateral section of the Achilles tendon was performed under sterile conditions in seven cats (2.5 to 3.5 kg body weight) with a sham operation on the contralateral side. After 28 to 42 days the monosynaptic response was recorded from the ventral roots L_7 and S_1 and from the dorsal surface of the cord to single-shock stimulation of gastrocnemius nerves (combined branches to medial and lateral head), the posterior tibial and peroneal nerves. The stimuli were maximal for the monosynaptic response. Conventional electrophysiological arrangements for recording and stimulating were used. In order to ascertain the symmetry of the monosynaptic reflex response, the latent period and amplitude on the right and left sides were compared in seven non-operated animals. Furthermore, the course of post-tetanic potentiation was registered, and the operated and non-operated sides were compared. First, experiments were performed in decapitated animals; later, when it was found that the results were not affected by the type of preparation, animals anesthetized by chloralose were used. In some cats *d*-tubocurarine was used. Results were evaluated statistically by the *t*-test.

Table 1. Latent period and amplitude mean values (± standard error) of the monosynaptic response in normal cats [*R*, right; *L*, left; $(\Sigma R/L)/n$, average percentage difference], and cats after unilateral section of the Achilles tendon (*T*, side of tenotomy; *C*, contralateral; $(\Sigma T/C)/n$, average percentage difference). Recorded from L_7 and S_1 ventral roots, (*n*, number of animals).

Record	Latent period (msec)				Amplitude (mv)			
	L_7	*n*	S_1	*n*	L_7	*n*	S_1	*n*
				Normal				
R	3.14±0.21	7	3.03±0.10	3	0.381± 0.145	7	0.890±0.625	3
L	3.19±0.22	8	2.97±0.05	3	0.408± 0.162	7	1.049±0.730	3
$\frac{\Sigma R/L}{n}$	101.0 ±2.14%	7	102.1 ±2.28	3	91.5 ±16.5%	7	89.7 ±6.4%	3
				Tenotomy				
T	2.81±0.09	7	2.79±0.14	2	0.523± 0.101	7	0.778± 0.570	3
C	3.03±0.12	7	2.94±0.09	2	0.247± 0.120	7	0.294± 0.245	3
$\frac{\Sigma T/C}{n}$	93.3 ±2.64%	7	94.7 ±1.70	2	371.0 ±88.4%	7	338.8 ±92.5%	3

There was a fair symmetry of the monosynaptic response in normal non-operated animals as far as the latent period is concerned. Far more variation was encountered in the amplitude of the monosynaptic response (see Table 1).

In the operated animals, there was without exception a shorter latent period of response on the side of tenotomy recorded from L_7 and S_1 ventral roots on stimulation of gastrocnemius nerves as compared with the contralateral side (statistically significant for $p<0.05$). The amplitude of the monosynaptic response was considerably increased on stimulation of the gastrocnemius nerves on the operated as compared with the non-operated side (average, 371.0 percent from ventral root L_7; 338.8 percent from ventral root S_1. These values are statistically significant for $p<0.01$ in the former and $p<0.05$ for the latter) (see Table 1). An example of these results is given in Fig. 1.

The duration of the post-tetanic potentiation to 30 sec of stimulation at 410 impulses per second of the gastrocnemius nerves on the operated side and the non-operated side, respectively, was the same, the return to initial values being reached in 3 to 5 min. No differences either in the monosynaptic response or in the duration of post-tetanic potentiation were found between the operated and non-operated sides on stimulation of the posterior tibial or the peroneal nerve.

It thus appears that chronic inactivation of proprioceptors by tenotomy leads to a shortening of the latent period and to an increase in the amplitude of the monosynaptic reflex response. This finding is in accord with the assumption based on indirect evidence presented by Thomsen, Altamirano, and Luco (*1*) indicating an increase in the myotatic reflex following section of the tendon.

Eccles and McIntyre (*2*), using a different method of inactivation of spinal synapses, have obtained results different from our own. Twenty-one to forty days after section of the dorsal roots distal to the spinal ganglion, they found a decrease of the monosynaptic response, a prolongation of the latent period and of post-tetanic potentiation on the operated side. These findings have recently been confirmed in analogous experiments in which the EPSP's of motoneurones were recorded intracellularly after section of muscle nerves (*3*). The different results obtained after tenotomy may indicate that the effect observed by the above authors is mainly due to changes in the afferent neurons corresponding to retrograde degeneration of the motor neurons (*4*) and not to disuse. On the other hand, it is necessary to point out that our assumption about the decrease of proprioceptive impulses from the muscle after tenotomy requires direct experimental analysis of the function of proprioceptors in a chronically tenotomized muscle.

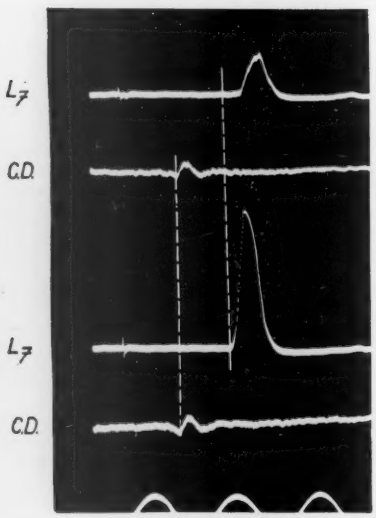

Fig. 1. Monosynaptic response recorded from ventral root L_7 and cord dorsum potential (*C.D.*) to single shock stimulation of gastrocnemius nerves in a cat 32 days after unilateral section of Achilles tendon, displayed on a double-beam cathode ray oscilloscope. Upper two traces: non-operated side; lower two traces: operated side. Time: 500 cy/sec. Note that there is no difference in the conduction time in the peripheral afferent pathways. The shorter latent period (0.31 msec) on the operated side can thus be attributed to a change in the central synaptic delay. The amplitude of the monosynaptic response of the operated side is 3.25 times larger than that of the non-operated side.

R. Beránek
P. Hnik
Institute of Physiology, Academy of Sciences, Prague, Czechoslovakia

References and Notes

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2. J. C. Eccles and A. K. McIntyre, *J. Physiol. (London)* **121**, 492 (1953).
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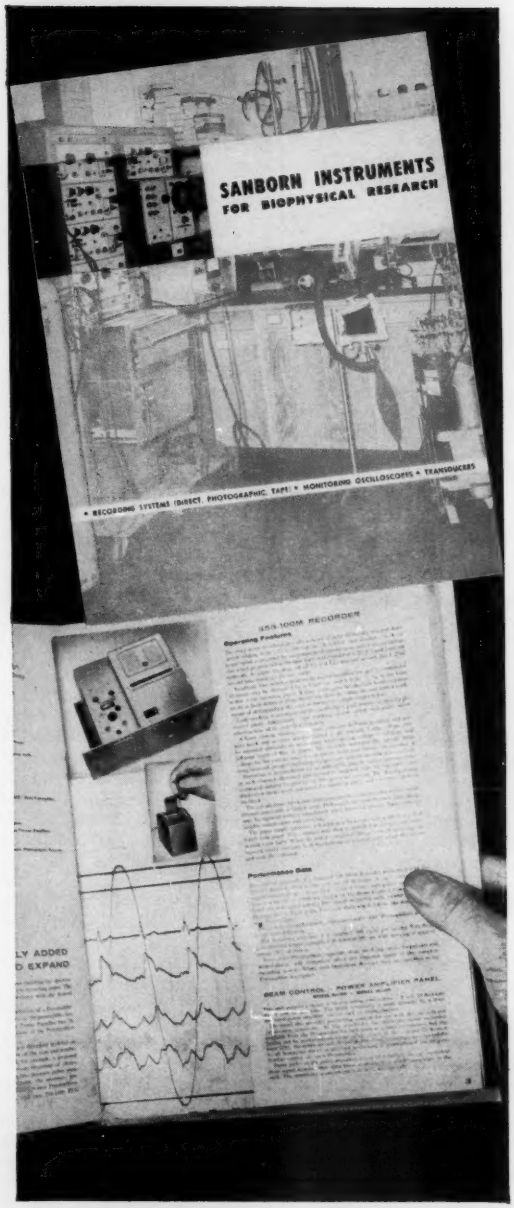
7 April 1959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Meetings

Forthcoming Events

November

10–12. Electrical Techniques in Medicine and Biology, 12th annual conf., Philadelphia, Pa. (L. E. Flory, RCA Laboratories, Princeton, N. J.)

10–15. Laboratory Measurement and Automation Techniques in Chemistry, intern. cong., Basel, Switzerland. (ILMAC, 61 Clarastrasse, Basel, Switzerland.)

11–12. Clinical Anticancer Drug Research, Washington, D.C. (B. H. Morrison, III, Cancer Chemotherapy National Service Center, National Cancer Inst., Bethesda 14, Md.)

11–13. Operations Research Soc., 16th natl., Pasadena, Calif. (J. L. Taylor, NORAIR Div., Northrop Corp., Hawthorne, Calif.)

11–14. Society of Naval Architects and Marine Engineers, annual, New York, N.Y. (W. N. Landers, SNAME, 74 Trinity Pl., New York 6.)

12–13. Cardiology in Aviation, intern. symp., Brooks Air Force Base, Tex. (L. E. Lamb, Dept. of Internal Medicine, School of Aviation Medicine, Brooks Air Force Base.)

12–13. Utilization of Atomic Energy, 2nd annual conf., College Station, Tex. (G. M. Krise, Radiation Biology Laboratory, Texas Engineering Experiment Station, College Station.)

12–18. International Odontological Session (with 64th Paris Dental Congress), Paris, France. (J. Charon, Secretary-General, 31, rue Tronchet, Paris 8e, France.)

15–18. Society of American Foresters, 59th, San Francisco, Calif. (Soc. of American Foresters, Mills Bldg., 17th and Pennsylvania Ave., NW, Washington 6.)

15–19. American Soc. of Agronomy, Cincinnati, Ohio. (L. G. Monthey, 2702 Monroe St., Madison 5, Wisc.)

15–20. Radiological Soc. of North America, conf., Chicago, Ill. (Radiological Soc. of North America, 815 Medical Arts Bldg., Fort Worth, Tex.)

16–18. Molecular Structure, 3rd conf., Houston, Tex. (Robert A. Welch Foundation, 2010 Bank of the Southwest Bldg., Houston 2.)

16–19. Magnetism and Magnetic Materials, 5th conf., Detroit, Mich. (D. M. Grimes, Dept. of Electrical Engineering, Univ. of Michigan, Ann Arbor.)

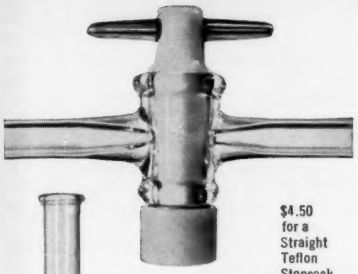
16–20. American Rocket Soc., annual meeting, Washington, D.C. (J. J. Harford, ARS, 500 Fifth Ave., New York 36.)

16–20. Automation Cong., 5th intern., New York, N.Y. (R. Rimbach, 845 Ridge Ave., Pittsburgh 12, Pa.)

16–21. Antarctic Symp., Buenos Aires, Argentina. (R. N. Panzarini, Instituto Antarctico, Argentino, Cerrito 148, Buenos Aires.)

16–21. Disposal of Radioactive Waste, conf., Monaco. (Intern. Atomic Energy Agency, 11–13 Kärntner Ring., Vienna 1, Austria.)

17-18. Air Transportation, natl., San Francisco, Calif. (Inst. of Aeronautical Sciences, 2 E. 64 St., New York 21.)



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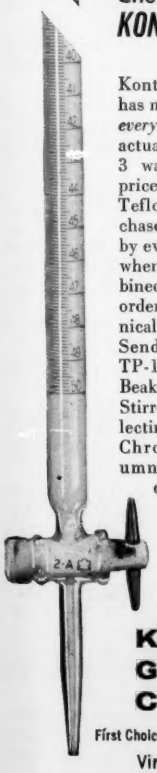

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17–19. Northeast Electronics Research and Engineering Meeting, Boston, Mass. (Miss S. Whiteker, Inst. of Radio Engineers, 73 Tremont St., Boston, Mass.)

17–20. National Assoc. for Mental Health, annual, Philadelphia, Pa. (American Psychiatric Assoc., 1700 18 St., NW, Washington 9.)

18. Association for Psychiatric Treatment of Offenders, New York, N.Y. (M. Schmideberg, New York Acad. of Sciences, 2 E. 63 St., New York 21.)

19–21. Inter-Society Cytology Council, annual, Detroit, Mich. (P. A. Younge, ISCC, 1101 Beacon St., Brookline 46, Mass.)

20–21. American Mathematical Soc., Winston-Salem, N.C. (J. W. Green, Univ. of California, Los Angeles 24.)

20–21. Nuclear Fusion, symp., Austin, Tex. (Texas Symp. on Nuclear Fusion, P.O. Box 8005, University Station, Austin.

22–24. American Soc. of Hematology, 2nd annual, St. Louis, Mo. (J. W. Rebuck, Henry Ford Hospital, Detroit, Mich.)

22–29. Pan American Child Cong., 11th, Bogotá, Colombia. (Office of Intern. Conferences, Department of State, Washington 25.)

23–24. Solid-State Techniques in Modern Instrumentation, symp., Philadelphia, Pa. (G. L. Eberly, 12 S. 12 St., Philadelphia 7.)

23–25. Fluid Dynamics (APS), Ann Arbor, Mich. (R. J. Emrich, Dept. of Physics, Lehigh Univ., Bethlehem, Pa.)

23–26. Technical European Conf. on Standards Applicable to Water (by invitation only), Copenhagen, Denmark. (World Health Organization, Regional Committee for Europe, 8 Scherfigsvej, Copenhagen.)

23–3. Inter-African Soils Conf., 3rd, Daloba, Guinea. (Committee for Technical Cooperation in Africa South of the Sahara, Abbey House, 2–8 Victoria St., London, S.W.1, England.)

25. Association for the Advancement of Psychoanalysis, New York, N.Y. (New York Acad. of Medicine, 2 E. 103 St., New York, N.Y.)

26–27. Association for the Utilization of Atomic Energy in Ship-Building and Navigation, Hamburg, Germany, Gesellschaft für Kernenergieverwertung in Schiffbau m.b.H., Hamburg.)

26–28. Central Assoc. of Science and Mathematics Teachers, Chicago, Ill. (G. G. Mallinson, Western Michigan Univ., Kalamazoo.)

26–28. Ceylon Assoc. for the Advancement of Science, Colombo. (K. Arumugam and S. Wijesundera, General Secretaries, Univ. of Ceylon, Colombo 3.)

26–29. Legal and Administrative Problems of Peaceful Use of Nuclear Energy, intern. conf., Rio Piedras, Puerto Rico. (J. Mayda, Faculty of Law, Univ. of Puerto Rico, Rio Piedras.)

27–28. American Mathematical Soc., Detroit, Mich. (J. W. Green, Univ. of California, Los Angeles 24.)

27–28. American Physical Soc., Cleveland, Ohio. (K. K. Darrow, Columbia Univ., New York 27.)

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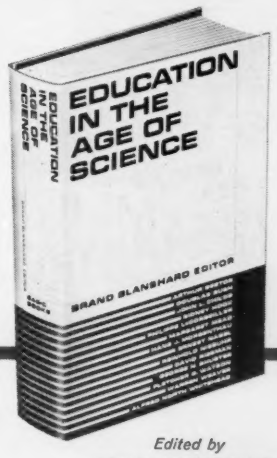

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27–17. Bahamas Medical Conf. Nassau. (B. L. Frank, Box 4037, Fort Lauderdale, Fla.)

29–30. American College of Chest Physicians, Dallas, Tex. (M. Kornfield, 112 E. Chestnut St., Chicago 11, Ill.)

29–4. American Soc. of Mechanical Engineers, annual, Atlantic City, N.J. (ASME, 29 W. 39 St., New York 18.)

30–2. American Acad. for Cerebral Palsy, 13th annual, Los Angeles, Calif. (G. L. Brooks, AACP, Brown Univ., Providence 12, R.I.)

30–2. French-Speaking Neurosurgeons Society, annual, Paris, France. (M. David, 4, rue Galliera, Paris.)

30–3. Eastern Joint Computer Conf., Boston, Mass. (Miss M. Fox, EJCC, Box 4999, Washington 8.)

30–3. Entomological Soc. of America (joint with the societies of Canada and Ontario), annual, Detroit, Mich. (L. L. Reed, Entomological Soc. of Canada, Science Service Building, Ottawa, Canada.)

30–16. Tropical Meteorology, symp., Nairobi, Kenya, East Africa. (Secretariat, World Meteorological Organization, Campagne Rigot, Avenue de la Paix, Geneva, Switzerland.)

30–17. Problems of Tropical Meteorology in Africa and the Neighboring Islands, symp., Nairobi, Kenya, Africa. (World Meteorological Organization, Campagne Rigot, 1, Avenue de la Paix, Geneva, Switzerland.)

December

1–3. Eastern Joint Computer Conf., Boston, Mass. (D. T. Ross, Dept. of Electrical Engineering, Massachusetts Inst. of Technology, Cambridge.)

1–4. American Medical Assoc. (clinical), Dallas, Tex. (R. M. McKeown, 510 Hall Bldg, Coos Bay, Oreg.)

2–4. Electrical Furnace Conf., Cleveland, Ohio. (E. O. Kirkendall, AIME, 29 W. 39 St., New York 18.)

3–4. Semiconductor Surfaces, 2nd conf., Silver Spring, Md. (R. F. Greene, U.S. Naval Ordnance Lab., White Oak, Silver Spring, Md.)

3–4. Vehicular Communications, St. Petersburg, Fla. (L. G. Cumming, IRE, 1 E. 79 St., New York 21.)

3–5. Corrosion, symp., Dresden, Germany. (Chemische Gesellschaft in der Deutschen Demokratischen Republik, Unter den Linden 68/70, Berlin W.8, Germany.)

3–5. Visual Communications, 3rd annual intern. conf., New York, N.Y. (E. Kaestner, Soc. of Reproductive Engineers, Bell Telephone Labs., New York, N.Y.)

3–11. Training and Education in Nutrition, European symp., Frankfurt am Main, Germany. (Food and Agricultural Organization of the United Nations, Viale delle Terme di Caracalla, Rome, Italy.)

3–12. International Confederation of Free Trade Unions, 7th world cong., Brussels, Belgium. (ICFTU, 24, rue du Lombard, Brussels.)

4–6. American Psychoanalytic Assoc., New York, N.Y. (D. Beres, 151 Central Park West, New York 23.)

5–10. American Acad. of Dermatology and Syphilology, Chicago, Ill. (R. R. Kierland, First National Bank Bldg., Rochester, Minn.)

6. American Acad. of Dental Medicine, mid-annual, New York, N.Y. (A. J. Cannistraci, 2152 Muliner Ave., New York 62.)

6–10. American Inst. of Chemical Engineers, annual, San Francisco, Calif. (F. J. Van Antwerpen, AICE, 25 W. 45 St., New York 36.)

7–12. Algology, UNESCO symp., New Delhi, India. (J. P. Correa, South Asia Cooperation Office, 21, Curzon Rd., New Delhi, India.)

8–10. Application of Electrical Insulation, 2nd natl. conf., Washington, D.C.) (N. S. Hibshman, AIEE, 33 W. 39 St., New York 18.)

9–15. American Acad. of Optometry, Chicago, Ill. (C. C. Koch, 1506–1508 Foshay Tower, Minneapolis 2, Minn.)

11–12. American Rheumatism Assoc., Detroit, Mich. (F. E. Demartini, Presbyterian Hospital, 622 W. 168 St., New York 32.)

11–12. Association for Research in Nervous and Mental Disease, annual, New York, N.Y. (R. J. Masselink, 700 W. 168 St., New York 32.)

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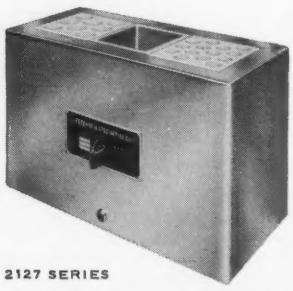

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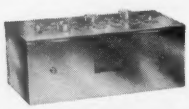

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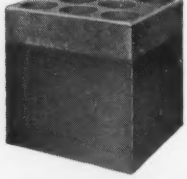

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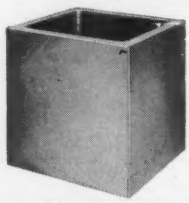

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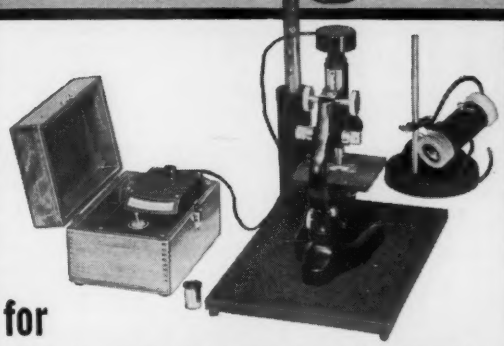

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11–12. Salt and Water Metabolism, symp., New York, N.Y. (A. P. Fishman, New York Heart Assoc., 10 Columbus Circle, New York 19.)

11–12. Texas Acad. of Science, Austin. (L. Kennamer, Dept. of Geography, Univ. of Texas, Austin 12.)

16–18. American Soc. of Agricultural Engineers, Chicago, Ill. (J. L. Butt, P.O. Box 229, St. Joseph, Mich.)

25–27. Indian Mathematical Soc., 25th conf., Allahabad, India. (B. N. Prasad, Allahabad Univ., Lakshmi Niwas, George Town, Allahabad 2.)

26–30. American Assoc. for the Advancement of Science, annual, Chicago, Ill. (R. L. Taylor, AAAS, 1515 Massachusetts Ave., N.W, Washington 5.)

The following 46 meetings are being held in conjunction with the AAAS annual meeting.

AAAS Committee on Science and the Promotion of Human Welfare (B. Commoner, School of Botany, Washington Univ., St. Louis 5, Mo.). 27 Dec.

AAAS Cooperative Committee on the Teaching of Science and Mathematics (Brother G. Nicholas, Dept. of Biology, Univ. of Notre Dame, Notre Dame, Ind.). 27 Dec.

Academy Conference (A. M. Winchester, Stetson Univ., De Land, Fla.), 27–28 Dec.

Alpha Epsilon Delta (M. L. Moore, 7 Brookside Circle, Bronxville, N.Y.). 29 Dec.

American Assoc. of Clinical Chemists (A. Dubin, Director of Biochemistry, Cook County Hospital, Chicago 12, Ill.). 26–27 Dec.

American Geophysical Union (W. C. Krumbein, Dept. of Geology, Northwestern Univ., Evanston, Ill.). 28 Dec.

American Meteorological Soc. (K. Spengler, 3 Joy St., Boston, Mass.).

American Nature Study Soc. (E. L. Will, State Univ. Teachers College, Oneonta, N.Y.). 26–30 Dec.

American Physiological Assoc. (F. A. Hitchcock, Ohio State Univ., Columbus). 28 Dec.

American Political Science Assoc. (J. Robinson, Dept. of Political Science, Northwestern Univ., Evanston, Ill.). 28 Dec.

American Psychiatric Assoc. (E. L. Bliss, General Hospital, Salt Lake City, Utah). 28–29 Dec.

American Soc. of Criminology (D. E. J. MacNamara, New York Inst. of Criminology, Inc., New York 36). 28–29 Dec.

American Soc. of Naturalists (A. D. Hasler, Dept. of Zoology, Univ. of Wisconsin, Madison). 27–28 Dec.

American Soc. of Plant Taxonomists (L. R. Heckard, Dept. of Botany, Univ. of Illinois, Urbana). 28–30 Dec.

American Sociological Soc. (J. S. Coleman, Dept. of Sociology, Univ. of Chicago, Chicago 37, Ill.). 28–29 Dec.

American Statistical Assoc. (R. F. Winch, Dept. of Sociology, Northwestern Univ., Evanston, Ill.). 29–30 Dec.

Association of American Geographers (A. Cutshall, Univ. of Illinois, Navy Pier, Chicago 11). 29 Dec.

Association for Computing Machinery (W. F. Cahill, Goddard Space Flight Center, Silver Spring, Md.). 29 Dec.

Astronomical League (E. Halbach, 2971 S. 52 St., Milwaukee 19, Wisc.). 26 Dec.

Beta Beta Beta (Mrs. F. G. Brooks, P.O. Box 515, Ansonia Station, New York 23). 27–28 Dec.

Chicago Acad. of Sciences (R. A. Edgren, Chicago Acad. of Sciences, 2001 N. Clark St., Chicago 14, Ill.). 29–30 Dec.

Conference on Scientific Communications (G. L. Seielstad, Applied Physics Lab., Johns Hopkins Univ., Silver Spring, Md.). 28–29 Dec.

Conference on Scientific Manpower (T. J. Mills, National Science Foundation, Washington 25). 28 Dec.

Ecological Soc. of America (W. C. Ashby, Dept. of Botany, Univ. of Chicago, Chicago 37, Ill.). 28–30 Dec.

Honor Soc. of Phi Kappa Phi (L. R. Guild, 634 S. Western Ave., Los Angeles 5, Calif.). 30–31 Dec.

Illinois Geographical Soc. (Miss M. Grant, Morton Junior College, Cicero, Ill.). 28 Dec.

Institute of Management Sciences (M. M. Flood, College of Engineering, Univ. of Michigan, Ann Arbor). 29 Dec.

Metric Assoc. (J. T. Johnson, Ravenswood YMCA, 1725 Wilson Ave., Chicago 40, Ill.).

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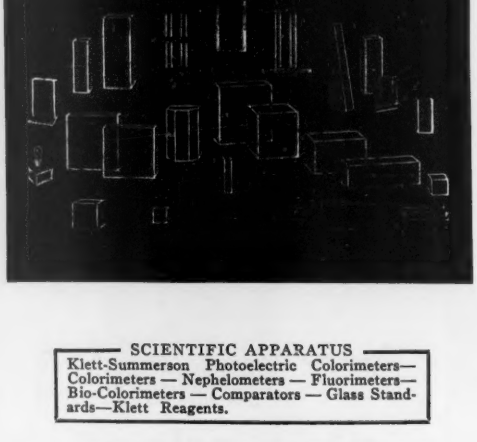

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Mycological Soc. of America (D. P. Rogers, Dept. of Botany, Univ. of Illinois, Urbana).

National Acad. of Economics and Political Science (J. Rothrock, Pan American Union, Washington 6). 29 Dec.

National Assoc. of Biology Teachers (H. E. Weaver, 202 Men's Old Gym, Univ. of Illinois, Urbana). 26–30 Dec.

National Assoc. for Research in Science Teaching (J. C. Mayfield, Univ. of Chicago, Chicago 37, Ill.). 26–30 Dec.

National Assoc. of Science Writers (P. Fraley, Evening Bulletin, Philadelphia, Pa.). 27 Dec.

National Geographic Soc. (W. R. Gray, NGS, 16 and M Sts., NW, Washington 6). 30 Dec.

National Science Teachers Assoc. (R. H. Carleton, NSTA, 1201 16 St., NW, Washington, D.C.). 26–30 Dec.

National Soc. for Medical Research (R. A. Rohweder, NSMR, 920 S. Michigan Blvd., Chicago 5, Ill.). 29 Dec.

National Speleological Soc. (T. C. Barr, Jr., Tennessee Polytechnic Inst., Cookeville, Tenn.). 28 Dec.

Philosophy of Science Assoc. (W. A. R. Ley, Roosevelt College, Chicago, Ill.). 28 Dec.

Scientific Research Soc. of America (D. B. Prentice, 56 Hillhouse Ave., New Haven 11, Conn.). 29 Dec.

Sigma Delta Epsilon (Miss E. S. Anderson, Stratford Hotel, 25 E St., NW, Washington, D.C.). 26–30 Dec.

Society for General Systems Research (R. L. Meier, Mental Health Research Institute, Univ. of Michigan, Ann Arbor).

Society for the History of Technology (M. Kronzberg, Dept. of History, Case Inst. of Technology, Cleveland, Ohio).

Society of the Sigma Xi (T. T. Holme, 56 Hillhouse Ave., New Haven 11, Conn.). 29 Dec.

Society of Systematic Zoology (R. E. Blackwelder, Southern Illinois Univ., Carbondale). 26–30 Dec.

Tau Beta Pi Assoc. (R. H. Nagel, Univ. of Tennessee, Knoxville). 27 Dec.

United Chapters of Phi Beta Kappa (C. Billman, 1811 Q St., NW, Washington, D.C.). 29 Dec.

27–30. American Anthropological Assoc., Mexico City. (W. S. Godfrey, Jr., Logan Museum, Beloit College, Beloit, Wisc.)

27–30. American Astronomical Soc., Cleveland, Ohio. (J. A. Hynek, Smithsonian Astrophysical Observatory, 60 Garden St., Cambridge 38, Mass.)

27–30. American Folklore Soc., Mexico City. (MacE. Leach, 110 Bennett Hall, Univ. of Pennsylvania, Philadelphia 4.)

27–30. American Statistical Assoc., Washington, D.C. (D. C. Riley, 1757 K St., NW, Washington 6.)

27–30. Institute of Mathematical Statistics (weather control), Washington, D.C. (J. Neyman, Statistical Lab., Univ. of California, Berkeley 4.)

28–29. American Chemical Soc. (Div. of Industrial and Engineering Chemistry), symp., Baltimore, Md. (M. A. H. Emery, ACS, 18 and K Sts., NW, Washington D.C.)

28–29. Industrial Relations Research Assoc., Washington, D.C. (E. Young, Sterling Hall, Univ. of Wisconsin, Madison.)

28–29. Mechanisms of Interfacial Reaction, American Chemical Soc., annual symp, Baltimore, Md. (H. E. Hoelscher, Chemical Engineering Dept., Johns Hopkins Univ., Baltimore, Md.)

28–29. Northwest Scientific Assoc., Spokane, Wash. (W. B. Merriam, Dept. of Geography, State College of Washington, Pullman.)

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28–30. Western Soc. of Naturalists, Los Angeles, Calif. (Y. U. Amrein, Dept. of Zoology, Pomona College, Claremont, Calif.)

28–31. Phi Delta Kappa, Columbia, Mo. (A. G. Clark, 316 Dalzell Ave., Ben Avon, Pittsburgh 2, Pa.)

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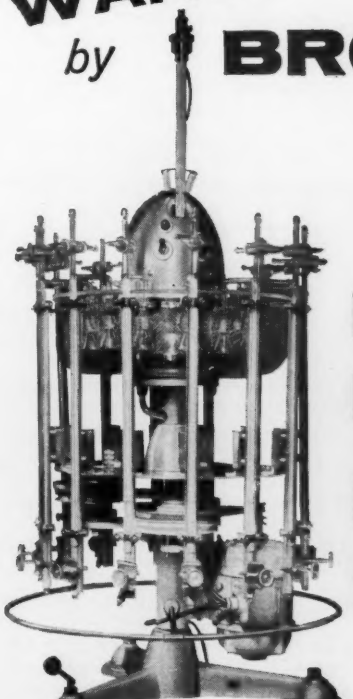

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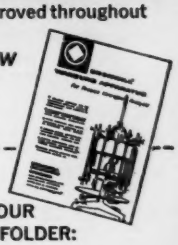

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Effective this year, the former General Program-Directory, which had become an unwieldy book of more than 400 pages, has been separated into *two* publications, namely:

a) The Directory of AAAS Officers and Activities, 96 pp., already published; and
b) The General Program of the Annual Meeting, c. 200 pp., which will appear early in December

Both of these, sold at cost, may be purchased separately—in advance (see coupon below), or at the meeting. Some of their *respective* contents are:

The General Program

1. The two-session general symposium "Moving Frontiers of Science IV," arranged by the Committee on AAAS Meetings.
2. Programs of the 18 AAAS sections (symposia and contributed papers).
3. Programs of the more than 80 participating societies.
4. Sessions of the Conference on Scientific Communication, Conference on Scientific Manpower, and the Academy Conference.
5. The Special Sessions: AAAS Address and Reception, National Geographic Society, Phi Beta Kappa, Sigma Xi, RESA, Tau Beta Pi Association.
6. Details of the Morrison Hotel—center of the Meeting—and of the other session sites.
7. Titles of the latest foreign and domestic scientific films to be shown in the AAAS Science Theatre.
8. Exhibitors in the 1959 Annual Exposition of Science and Industry and descriptions of their exhibits.

The Directory

1. AAAS officers, staff, committees, for 1959.
2. Section committees and other AAAS Council members.
3. The 285 affiliated organizations.
4. Historical sketch and organization of the Association.
5. Complete roll of AAAS presidents and their fields.
6. Publications of the Association, including all symposium volumes.
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■ PIPETTER permits normal finger-action control with suction provided by bulb. The operator's finger is accommodated by a tube sealed with a finger cot. The device accommodates the range of standard pipettes made for ordinary hand use. (Scientific Glass Apparatus Co., Dept. 115)

■ VOLTMETER for high-voltage measures directly positive and negative peaks to 150 kv and root-mean-square potentials to 115 kv. The instruments are portable and are equipped with built-in high-voltage multipliers for full-scale ranges of 75 kv. For higher voltage, the multiplier bushing is separately mounted. Single- and multiple-range models are available. (Associated Research, Dept. 134)

■ ANALYTICAL EVAPORATOR accommodates six samples in 50-ml erlenmeyer flasks, or 12 in test tubes. The apparatus consists of a stand, sample holder, gas manifold, and 12 gas injectors with individual needle-valve control. A thermostatted water bath permits evaporation at constant temperature, which may be set between 35° and 70°C. Dry air or nitrogen at flow rates up to 0.25 ft^3/min is required. (Organomation Associates, Dept. 123)

■ MICROSCOPES in a new line of 15 models include a home-laboratory series with two models; a medical series of five models, including a binocular microscope with full staging equipment and magnification up to 2000; a stereoscopic series of three models, available also as focusing head assembly only; a portable series of three models with self-contained battery-powered illumination; and two all-purpose models. (D. P. Bushnell and Co., Dept. 126)

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■ TENSILE TESTER is a portable device for tensile tests on round or flat specimens. The load is applied to the specimen by manual rotation of a knurled knob. The applied load is measured by a trapped-oil system and indicated on a 4½-in. gage. The testers are available in capacities from 100 to 1000 lb. Interchangeable jaws cover flat specimens of thickness up to ⅜ in. and round specimens of diameter from ⅛ to ⅝ in. Maximum specimen length is 7 in. Tester dimensions are 5 by 23 by 11 in.; weight is 36 lb. (Steel City Testing Machines, Inc., Dept. 137)

■ SPECTROMETER may be used for alpha, beta, gamma, or neutron detection by direct interchange of detecting crystals. Included are a 1.5 by 2 in. NaI (T1) crystal, photomultiplier tube, amplifier, pulse-height analyzer, count-rate meter, and pulse generators. The instrument is battery-operated and portable. (Radiation Instrument Development Laboratory, Dept. 116)

■ FREQUENCY METER of heterodyne type reads frequency directly from 100 to more than 10,000 Mcy/sec. Accuracy of ±0.03 percent is claimed. Accuracy at 5 Mcy/sec crystal check points is ±0.002 percent. Input sensitivity at 500 Mcy/sec and above is −30 dbm and at 100 Mcy/sec −5 dbm. The bandwidth of the video amplifier is 0.8 Mcy/sec. (Polytechnic Research and Development Co., Dept. 128)

■ TEMPERATURE-CONTROL SYSTEM provides continuous automatic control of liquid and air baths to a tolerance said to be ±0.1°C. The system is based on a transistorized crystal-controlled oscillator circuit that senses the position of the column in a mercury thermometer by means of an external electrode. The oscillator actuates a pulse-duration modulated system to control power up to 1500 watts. (Milltown Instrument Co., Dept. 129)

■ VIBRATION INTERFEROMETER for calibration of accelerometer vibration transducers consists of the interferometer proper, a multibeam stroboscopic slit assembly with white-light source, and a vibration generator. Frequency range is approximately 450 to 10,000 cy/sec. Double amplitudes over a range of 1 to 1000 μin. can be determined with accuracy said to be ±1 μin. or ±1 percent, whichever is greater. (Gaertner Scientific Corp., Dept. 133)

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■ DROPPING-MERCURY ELECTRODE contains a stable half cell which enables the test vessel to be rotated for quick change of sample solution. A ceramic frit liquid bridge provides low electrolytic resistance. The electrode combines in a compact unit the dropping-mercury system, constant-head mercury column, test vessel, reference electrode, reference salt bridge, water bath, and gas flowmeter. Fifty grams of mercury are required for operation. Mercury mass-flow rate can be determined while analysis is being made. (Leeds & Northrup Co., Dept. 142)

■ PIPETTE CONTROLLER can be operated with equal ease by right or left hand. Precision is said to permit fractional drop delivery to 0.01 ml. Construction material is chrome-plated metal and acid resistant gum rubber. (Tenso-Lab., Dept. 162)

■ THERMOELECTRIC JUNCTIONS are designed to maintain a temperature above or below ambient. The thermojunctions are made of cast semiconductors. In normal room ambient temperatures it is said to be possible to obtain a temperature difference in excess of 40°C with an input power of 2 watts. As a generator the junction can produce approximately 0.25 watt electrical output with a difference of temperature of 150°C between cold and hot junctions. Maximum hot junction temperature is 150°C; minimum cold junction temperature is −75°C. Resistance is 0.0025 ohm. Maximum current is 40.0 amp. (Ohio Semiconductors, Inc., Dept. 138)

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■ HIGH-VOLTAGE POWER SUPPLY produces 16 kv d-c at 200 μa from input of 26.5 volts d-c, 650 ma. Conversion is through a mechanical vibrator, transformer, and voltage doubler. The unit can operate at ambient temperatures from −65° to +125°F. Dimensions are 4⅞ by 6⅜ by 6⅞ in. (Southwestern Industrial Electronics Co., Dept. 148)

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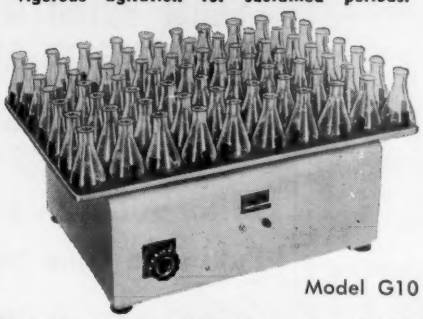

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EVOLUTION OF NERVOUS CONTROL FROM PRIMITIVE ORGANISMS TO MAN

AAAS Symposium Volume No. 52

Editor Allan D. Bass

Published June 1959

6" x 9", 240 pp., 61 illus., references, index, cloth
AAAS members' cash orders $5.00,
Retail $5.75

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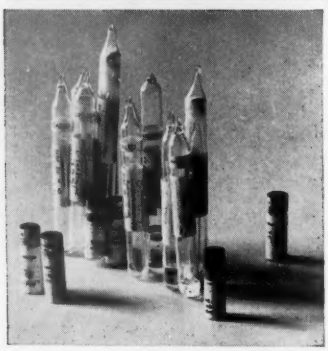

This handsome little still life illustrates the high quality and variety of radioactive carbon reagents now available from us for your research work. Today we offer over 250 different carbon-14 compounds, and dozens of phosphorus-32, sulfur-35, and tritium compounds. All are listed with prices and package sizes in our chemical catalog "Schedule E." In this new 20 page schedule you'll also find high intensity beta and gamma sources, reference sources, radioactive standards, and source kits. If you're interested in radioactivity you'll want a copy. It's absolutely free and there's no obligation. If you don't have a copy of our General Catalog R to go along with the "Schedule E," ask for that, too. This illustrates and describes all of the radioactivity measuring instruments made by us.

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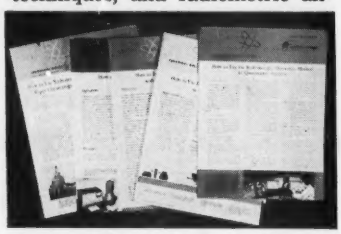
Companies investing in radioisotopes, either for process control or research, averaged more than an eight-fold return on their money according to a recent NICB report. Biggest savings were reported by the chemical and petroleum industries where $500,000 invested brought a 12-month savings of more than $8,000,000. The report pointed out that although returns were juicy, only a small number of companies use radioisotopes.

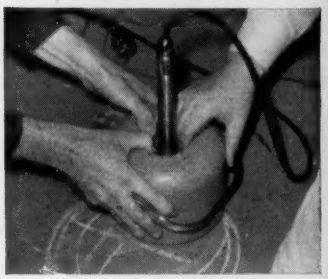
We think it will pay you to investigate the uses of radioisotopes in *your* research laboratories. To help familiarize you with the ways isotopes are being used profitably today, we have prepared a series of Technical Bulletins. Six have been completed. They describe common process applications of radioactivity such as mixing evaluation studies, and review laboratory applications including isotope dilution analysis, paper radiochromatography techniques, and radiometric analysis. Why don't you write asking us to send you the first six Technical Bulletins? Read them, and if you think they are helpful we'll gladly put your name on our mailing list to receive them regularly. They're meaty, short, and (we think) stimulating. The cost? Only a postcard.



LEAKY PIPES?

Radiant heating systems are nice, but when they start to leak, it can be mighty hard to find the trouble. We were called in recently to help locate a leak somewhere in 2640 feet of pipe in an elementary school. The pipes, embedded 6″ in concrete, ran up and down the halls, under walls and furniture. Several previous attempts to find the leak were unsuccessful and had left ugly torn-up floor areas.

In cooperation with a plumbing contractor, we drained the 160 gallon system, then pumped into the empty system another 160 gallons of water made slightly radioactive with radiosodium-24. The entire floor area was then monitored with Geiger and scintillation detectors. The general area of the leak was located within 30 minutes. Standard Nuclear-Chicago instruments were then used to pinpoint the leak within



½ inch. A couple of tiles were removed, the pipe exposed and repaired. Probably to the disappointment of the small fry, the whole job was completed on a Saturday afternoon.

Although we're not in the plumbing business, we'll be glad to forward any inquiries you may have on this application to our plumbing friends who now have authorization from the AEC to conduct these tests. Other process or research applications of radioisotopes we'll be happy to handle ourselves.

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